BRIEF AND ADDENDUM FOR APPELLEE DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

United States Court of Appeals
for the Federal Circuit

05-1184
(Serial No. 09/674,002)

IN RE MARTIN BILLGER AND MIKAEL BRULLS

Appeal from the United States Patent and Trademark Office,
Board of Patent Appeals and Interferences

JOHN M. WHEALAN
Solicitor

HEATHER F. AUYANG
LINDA MONCYS ISACSON
Associate Solicitors

P.O. Box 15667
Arlington, Virginia 22215
(571) 272-9035

Attorneys for the Director of the United States Patent and Trademark Office

May 11, 2005

Representative Claim

1. A stable, liquid pharmaceutical formulation of human parathyroid hormone at a concentration of 0.3 mg/ml to 10 mg/ml, comprising

(i) human parathyroid hormone,

(ii) a pharmaceutically acceptable buffer of pH 4 to 6,

(iii) NaCl,

(iv) mannitol,

(v) a preservative, and

(vi) water.

A67 (emphasis and spacing added).

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

STATEMENT OF RELATED CASES

(a) The Director is not aware of any other appeal involving the underlying decision in this case that was previously before this or any other appellate court.

(b) The Director is also not aware of any pending case in this or any other court that will directly affect, or be directly affected by, this Court's decision in this appeal.

BRIEF AND ADDENDUM FOR APPELLEE DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

United States Court of Appeals
for the Federal Circuit

05-1184
(Serial No. 09/674,002)

IN RE MARTIN BILLGER AND MIKAEL BRULLS

Appeal from the United States Patent and Trademark Office,
Board of Patent Appeals and Interferences

I. STATEMENT OF THE ISSUE

The key issue in this case involves the addition of "salt" to parathyroid hormone ("PTH") compositions. Billger's[1] claims are directed to a composition containing PTH and other additives for the treatment of bone-related disorders, such as osteoporosis. The additives, *inter alia*, facilitate administration of the PTH composition to a patient. Billger alleges that the addition of salt to the claimed PTH composition distinguishes the alleged invention from the prior art.

---

[1] Throughout this brief, inventors Billger and Brulls are referred to collectively as "Billger," the Joint Appendix is referred to as "A__," the Addendum to the Director's Brief is referred to as "ADD__," and Billger's Brief is referred to as "Br. at __."

However, the Board affirmed the obviousness rejection of the claims finding that adding salt to PTH compositions was taught by both prior art references (Holthuis or Endo). The key issue on appeal is whether substantial evidence supports the Board's findings that a person of ordinary skill would have known to add salt to PTH compositions.

II. STATEMENT OF THE CASE

Billger's application was filed on or around December 27, 2000 and claims priority to a PCT application filed on or around April 26, 1999. The Board affirmed the Examiner's rejection of claims 1-7, 9, 12, 17, 18, 21-24, 26-28 and 31-36 (A33-36) as obvious in view of Holthuis et al. ("Holthuis"), U.S. Patent No. 5,496,801 (A71-78), and Endo et al. ("Endo"), U.S. Patent No. 5,563,122 (A79-83). A2. The Board also affirmed the Examiner's rejections of claims 20 and 25 as obvious in view of Holthuis, Endo and Selsted, U.S. Patent No. 5,547,939 (A101-116). *Id.*

Billger now appeals that decision to this Court. Because Billger has expressly chosen not to argue the claims separately on appeal and not to separately appeal the rejection of claims 20 and 25 (Br. at 16, n.5; A25), this appeal is directed only to representative claim 1.

III. STATEMENT OF THE FACTS

A. Claim 1

PTH is a protein well recognized for controlling bone growth and density (A156); however, proteins may aggregate or precipitate, which is undesirable (A157, lines 1-9). Billger's specification (A156-178) notes that protein aggregation and precipitation may be rapid or slow (A157, lines 1-8) and can be determined by visual inspection (A162, lines 26-27). Billger's claimed invention is directed to a "stable" liquid containing PTH and other additives, including salt. A67-70.

Representative claim 1 reads as follows:

> 1. A stable, liquid pharmaceutical formulation of human parathyroid hormone [PTH] at a concentration of 0.3 mg/ml to 10 mg/ml, comprising
>
> (i) human parathyroid hormone,
>
> (ii) a pharmaceutically acceptable buffer of pH 4 to 6,
>
> (iii) NaCl [sodium chloride or salt],
>
> (iv) mannitol [sugar],
>
> (v) a preservative, and
>
> (vi) water.

A67 (emphasis, spacing and bracketed information added). The formulation may be prepared in liquid form and is then either: (i) administered, or (ii) freeze-dried (lyophilized) and reconstituted prior to administration. A159, lines 4-6; A161, lines 5-8. Billger's specification teaches that preservatives allow for "the use of the formulation in a multidose product." A167.

The terms "stable, liquid" were added to the claim by an amendment filed after the final rejection in an attempt to distinguish the claimed composition from the prior art. A44; A268-69. However, Billger's specification does not expressly define the term "stable" and does not teach a minimum time for determining "stability." Moreover, none of the more than 30 compositions in Examples 1-6 testing "stability" fall within the limitations of the claim. A163-72. For example, none contained a "preservative," except for Example 6, which lacked salt or mannitol. A166-67. Additionally, Example 1 compositions 2A, 2B, and 2C each lacked salt and 2D, 2E, 2F, and 2H each lacked mannitol (A169); Example 2 tested compositions for "pH Stability" with a PTH concentration of 0.2 mg/ml and no salt (A163-64); Examples 3 and 4 tested compositions with a PTH concentration of 0.2 mg/ml (A164-65); and Example 5 tested compositions with a PTH concentration of 0.25 mg/ml and no mannitol (A165).

B. The Prior Art

1. Holthuis

Holthuis (A71-78) teaches using a formulation containing human PTH at a concentration of 0.09 mg/ml to 2.27 mg/ml (A77, col. 6, lines 26-30 (*e.g.*, the concentration (mg/ml) of 100 μg PTH in 1.1 ml is 0.1 mg ÷ 1.1 ml = 0.09 mg/ml)); *see also* A211; A244; A41; A45; A49; A51) for the treatment of bone-related disorders, such as osteoporosis (A76, col. 4, lines 28-30 ("[o]steoporosis therapy entails administration of the reconstituted [PTH] preparation by injection . . . . ")). Holthuis also teaches the desirability of using certain pharmaceutically acceptable buffers, preferably citrate-based buffers (pH 3.5 to 7.5), particularly when the PTH preparation is administered directly after reconstitution. A76, col. 3, line 61 to col. 4, line 8; *see also* A77, col. 6, lines 26-28 (teaching a buffer of pH 4 and 6).

Holthuis describes PTH compositions (either freeze-dried or liquid) containing mannitol, including an "International Reference preparation" found in *Martindale, The Extra Pharmacopoeia*, The Pharmaceutical Press, London, 29th edition, 1989 ("Martindale 1989"). A75, col. 1, lines 44-64. Moreover, Holthuis specifically teaches that certain sugars, such as lactose and maltose, should be avoided and that polyol-type (sugar alcohol) is preferred, specifically mannitol, because, *inter alia*, "mannitol itself confers some stability to the PTH in solution."

A76, col. 3, lines 32-47; *see also* A76, col. 4, lines 17-19 ("Most preferably . . . the excipient is 5% mannitol (w/v)").

Holthuis teaches using preservatives with the PTH composition if after reconstitution it is used for over several days. A77, col. 5, lines 52-56 ("[i]n the case-where a multi-dose vial is provided, a bacteriostatic agent should be incorporated, and the formulation remaining after administration of each dose can be refrigerated for subsequent use within a time frame of several days").

Importantly, Holthuis teaches a PTH formulation that is prepared in liquid form, freeze-dried (A71 (abstract); *see also* A75, col. 2, lines 27-32) and then reconstituted using either salt water (saline) (A75, col. 1, lines 32-35 ("Most [PTH compositions] are prepared in water-based vehicles such as saline . . . .") (emphasis added); *see also* A75, col. 1, lines 53-54 ("a human PTH(1-38) preparation reconstituted into a saline vehicle")) or water (A75, col. 2, lines 33-44; A77, col. 5, lines 25-28 ("[t]he PTH preparations of the present invention are complete in the sense that the end-user need reconstitute the preparation solely in sterile water to generate an administrable formulation")).

2. Endo

Endo teaches the desired benefits of adding salt to human PTH compositions containing mannitol before freeze-drying. A79-83. Specifically,

Endo teaches that although mannitol is the "conventional stabilizing agent" used for PTH compositions (A80, col. 1, lines 20-23), this stabilizing effect was "unsatisfactory" (A80, col. 1, lines 22-24), and for that reason Endo discovered that "unexpectedly dramatically improved stability" was obtained by the addition of salt with mannitol (A80, col. 1, lines 29-34). As a result, Endo explains that "excellent heat stable [freeze-dried] preparations of PTH can be prepared using a combination of sugar and [salt] as stabilizing agents." A80, col. 1, lines 35-37.

Importantly, Endo even warns against the addition of too much salt. A80, col. 2, lines 15-18 ("when the amount of sodium chloride [salt] exceeds 20% of the weight of sugar, a lyophilized cake of the preparation will suffer shrinkage and the stability tends to decrease"). Accordingly, Endo teaches that the amount of salt added is preferably from about 1/100 to 1/10 weight part per weight part of sugar (A80, col. 2, lines 18-21), *e.g.*, Example 3 discloses a PTH composition containing 2 mg/ml salt and 20 mg/ml mannitol dissolved in water (A81, col. 3, lines 15-22).

In particular, Endo teaches combining PTH, mannitol and salt with water, pharmaceutically acceptable buffers, and preservatives before freeze-drying (A80, col. 2, lines 23-35) and then using water to reconstitute for injection (A80, col. 2, lines 23-24).

C. The Board Decision

The Board agreed with the Examiner that Holthuis and Endo teach human PTH compositions that may be prepared in liquid form, then freeze-dried and later reconstituted using salt water or water. A3-4; A41. Specifically, Holthuis teaches a pharmaceutical formulation containing PTH (at a concentration of 0.09 mg/ml to 2.27 mg/ml), buffer (pH 4 to 6), and mannitol. A3. The Board agreed that Holthuis teaches using a preservative, such as a bacteriostatic agent, particularly when the liquid formulation is refrigerated for subsequent use over several days (A3; A41), thereby teaching a liquid PTH formulation which is "stable" for several days (A6; A45).

The Board also agreed with the Examiner that, motivated by the teachings of the references themselves, there are at least two ways one of ordinary skill would have been motivated to add salt to PTH compositions. A4-5; A41-42. One would have combined the freeze-dried PTH composition taught by Holthuis with salt water, which would yield the claimed "stable, liquid" pharmaceutical composition with a reasonable expectation of success, because Holthuis teaches that most PTH compositions are reconstituted using salt water. A4; A41-42. Alternatively, the Board agreed that one would have found it desirable to add salt to the freeze-dried PTH formulations of Holthuis with a reasonable expectation of

success because Endo teaches the desirability of adding salt, in the presence of mannitol, to further stabilize PTH. A4; A42. The Board also agreed that using water to reconstitute a freeze-dried PTH composition containing salt would yield a liquid pharmaceutical formulation with salt water as required by claim 1. *Id.*

The Board found Billger's arguments that the prior art "taught away" from adding salt to PTH compositions unpersuasive. A6-8. In considering Billger's evidence, the Board recognized the well-established rule that "[w]hen prior art contains apparently conflicting references, the Board must weigh each reference for its power to suggest solutions to an artisan of ordinary skill." A7 (citing *In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991)).

First, the Board found that the two references (Holthuis and Endo) expressly teach the use of salt with PTH compositions. A3-5. As to the two references Billger relied on, the Board found they were not persuasive. A6-8. Specifically, the Board found that Billger's reliance on the outdated version of Martindale unhelpful. A6-7. Although Martindale 1989 suggested that salt should not be added to PTH compositions, its later-edition published in 1996, *Martindale, The Extra Pharmacopoeia*, The Pharmaceutical Press, London, 31st edition, 1996 ("Martindale 1996") (ADD12-19), did not include the same language (A138). Given that Billger's application was filed in 2000 and claims priority to a PCT

application filed in 1999, the Board found the 1996 version of Martindale more relevant. A6-7.

As for Billger's reliance on Canadian Patent Application No. 2,234,724 ("'724 application") – which is just that, an application – the Examiner observed that the statements in the '724 application attempting to discredit Endo were unsupported and contradicted by the application itself. A51-52. Specifically, while the '724 application states that dimers may form in compositions containing PTH, sugar and salt (A85), the Examiner found no quantitative data in the specification and absolutely no teachings on the formation of dimers when the PTH preparation is stored over a few days, either in liquid or freeze-dried form (A52). Furthermore, rather than showing a loss of PTH, the closest example to the teachings of Endo found in the '724 application showed no loss of PTH over a period of 1 or 3 months. A96 (Example 7); A51-52. Moreover, the Board found that Endo taught the combination of salt and mannitol (as claimed by Billger), as opposed to the salt and sucrose composition purportedly tested in the '724 application. A7-8. Based on this evidence, the Board found Billger's reliance on the '724 application to discredit Endo unpersuasive. *Id.*

Finally, the Board rejected Billger's belated attempt after the final rejection to distinguish the prior art by adding the phrase "stable, liquid" to the claim. A5-

6. Specifically, the Board was unconvinced by Billger's argument that the teachings of Holthuis and Endo are limited to "stable" dried compositions, rather than the claimed "stable" liquid compositions. A5. The Board found that while Holthuis and Endo teach freeze-dried PTH compositions, each reference specifically teaches reconstitution of the freeze-dried preparations into liquid form before administration and "[t]hus, the combination clearly teaches a liquid pharmaceutical formulation." *Id.* The Board then focused on the definition of the claim term "stable." *Id.* During prosecution, claims are given their broadest reasonable interpretation consistent with the specification. A5-6 (citing *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989)). The Board found that Billger's specification provides no explicit meaning or time period to define the term "stable" (A5-6; A44-45; A51), but discloses examples relating to the "stability" of PTH compositions starting at "zero" days (A5-6). Therefore, the Board reasoned that the term "stable" would encompass a composition two to three days after reconstitution (as taught by Holthuis). A5-6. Accordingly, the Board found that the prior art "combination does teach a stable, liquid pharmaceutical formulation having the recited components." A6.

IV. SUMMARY OF THE ARGUMENT

Besides the claim element requiring salt, it is undisputed that the prior art (Holthuis and Endo) teach PTH compositions containing every element of claim 1. However, the Board correctly found that each reference would have motivated one of ordinary skill to add salt to PTH compositions because: (i) Holthuis expressly teaches that salt water is commonly used to reconstitute freeze-dried PTH compositions; and (ii) Endo specifically teaches the desired benefits of adding salt to PTH compositions, particularly those taught by Holthuis. Thus, based on these teachings, one would have been motivated to add salt to PTH compositions, establishing a *prima facie* obviousness case.

Moreover, following *Young* the Board carefully weighed Billger's evidence of "teaching away" and found such evidence unpersuasive after reviewing the entire record. Specifically, the Board found that Holthuis and Endo teach the addition of salt to PTH compositions. On the other hand, the Board found the outdated Martindale 1989 less relevant than the more contemporaneous Martindale 1996 (which is closer to Billger's filing date) and the '724 application contradicted by the data (or lack thereof) in the application itself which did not persuasively discredit Endo.

Finally, Billger's belated attempt to amend the claim to add the phrase "stable, liquid" to distinguish over the prior art is unavailing because the prior art teaches a "stable, liquid" composition when any of the following events occur: (i) salt water is added to Holthuis' freeze-dried compositions for reconstitution, as expressly instructed by the reference itself; (ii) salt is added to the liquid preparation of Holthuis' compositions before freeze-drying, as taught by Endo; or (iii) salt is added to Holthuis' compositions before freeze-drying, then freeze-dried, and later reconstituted using water, as taught by either Holthuis or Endo. Any of these situations would result in a "stable, liquid" PTH composition containing buffer, salt, mannitol, preservative, and water meeting the literal terms of claim 1.

Accordingly, Billger's selective citation from the prior art references, which when read in their entirety clearly disclose and motivate one to make the claimed composition, cannot overcome the substantial evidence supporting the Board's underlying factual findings leading to the conclusion of obviousness.

V. ARGUMENT

A. Standard of Review

The ultimate issue of obviousness is a legal question based on underlying factual findings. *See In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000). What

the prior art teaches, including whether it teaches toward or away from the claimed invention, is a question of fact. *Para-Ordnance Mfg. v. SGS Importers Int'l, Inc.*, 73 F.3d 1085, 1088 (Fed. Cir. 1995). Similarly, whether a person of ordinary skill in the art would have been motivated to combine references is a question of fact. *Gartside*, 203 F.3d at 1316.

On appeal, the Board's factual findings are reviewed for substantial evidence. *Gartside*, 203 F.3d at 1315. Substantial evidence "is something less than the weight of the evidence but more than a mere scintilla of evidence," *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000) (citations omitted), and "means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion," *Consolidated Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938). As this Court recently stated, "where two different, inconsistent conclusions may reasonably be drawn from the evidence in record, an agency's decision to favor one conclusion over the other is the epitome of a decision that must be sustained upon review for substantial evidence." *In re Jolley*, 308 F.3d 1317, 1329 (Fed. Cir. 2002).

The proper interpretation of the claims is a question of law reviewed *de novo* on appeal. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998) (en banc). However, since claims during prosecution must be given their

"broadest reasonable interpretation," this Court reviews the USPTO's interpretation of disputed claim language to determine whether it is "reasonable in light of all the evidence before the Board." *In re Morris*, 127 F.3d 1048, 1055 (Fed. Cir. 1997).

B. The Board Properly Held That Claim 1 Would Have Been Obvious in View of Holthuis and Endo

1. All the Elements of Claim 1 are Taught by Holthuis and Endo

Claim 1 recites a "stable, liquid pharmaceutical formulation" comprising: (i) PTH (at a concentration of 0.3 mg/ml to 10 mg/ml); (ii) buffer (pH 4 to 6); (iii) NaCl (salt); (iv) mannitol (sugar); (v) preservative; and (vi) water. Except for salt, it is undisputed that Holthuis and Endo teach a PTH composition containing all the elements of the claim. A158, lines 5-9; Br. at 7. For example, Holthuis teaches a PTH concentration of 0.09 mg/ml to 2.27 mg/ml (A77, col. 6, lines 26-30),[2] which overlaps with the claimed range. Further, Holthuis (A76, col. 3, line 61 to col. 4, line 8; *see also* A77, col. 6, lines 26-28) and Endo (A80, col. 2, lines 23-35) teach using a pharmaceutically acceptable buffer of pH 4 to 6. Holthuis

---

[2] Billger has never disputed the Examiner's findings during prosecution that Holthuis teaches compositions containing PTH at a concentration of 0.09 mg/ml to 2.27 mg/ml. A211; A244; A41; A45; A49; A51.

(A75, col. 1, lines 44-64; A76, col. 3, lines 32-47; *see also* A76, col. 4, lines 17-19) and Endo (A80, col. 1, lines 20-23) also teach PTH compositions containing mannitol. Additionally, Holthuis (A77, col. 5, lines 52-56) and Endo (A80, col. 2, lines 23-35) teach the use of preservatives. Holthuis (A77, col. 5, lines 25-28) and Endo (A80, col. 2, lines 23-24) also teach adding water to reconstitute freeze-dried PTH compositions for injection.

2. Holthuis and Endo Each Teach Adding Salt to PTH Compositions

To sustain an obviousness rejection based on a combination of prior art, there must be some teaching, suggestion, or motivation supporting the combination. *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). The suggestion or motivation to combine the references may flow from any one of three sources: (1) the teachings of the prior art; (2) the knowledge of one skilled in the art; or (3) the nature of the problem to be solved. *SIBIA Neurosciences, Inc. v. Cadus Pharmaceutical Corp.*, 225 F.3d 1349, 1356 (Fed. Cir. 2000).

As the Board correctly found, both Holthuis and Endo provide multiple reasons to motivate one of ordinary skill to add salt to PTH compositions. A3-5. For example, Holthuis teaches that most freeze-dried PTH compositions are reconstituted using salt water. A75, col. 1, lines 32-35 ("Most [PTH

compositions] are prepared in water-based vehicles such as saline . . . .") (emphasis added) ; *see also* A75, col. 1, lines 53-54 ("a human PTH(1-38) preparation reconstituted into a saline vehicle") (emphasis added). Moreover, Endo specifically teaches the desired benefits of adding salt to PTH compositions containing mannitol (*i.e.*, the compositions taught by Holthuis) because by adding salt, "dramatically improved stability" for PTH compositions is obtained. A80, col. 1, lines 29-34. Following these teachings, the Board found that logically, one of ordinary skill would have found it desirable to add salt to a PTH composition. A4-5.

Thus, this obviousness rejection is simple and straightforward. As the Examiner correctly observed, "the claims are drawn to a composition, not a method of making the composition" and therefore "[i]t does not alter the composition itself when and how the composition becomes liquid form." A47. Accordingly, one would be motivated to add salt to a PTH composition by either: (i) adding salt water to Holthuis' freeze-dried PTH compositions for reconstitution, as expressly instructed by the reference itself; (ii) adding salt to Holthuis' liquid compositions before freeze-drying, as taught by Endo; or (iii) adding salt to Holthuis' liquid compositions before freeze-drying, then freeze-dry, and later reconstitute using water, as taught by either Holthuis or Endo. The result

in each case is the claimed invention, *i.e.*, a stable, liquid PTH formulation containing buffer, salt, mannitol, preservative, and water.

Billger argues lack of motivation because the prior art does not teach or suggest reconstituting Holthuis' freeze-dried PTH compositions with salt water. Br. at 8 and 37; *see also* Br. at 42-43. Billger argues that Holthuis teaches that only water may be used to reconstitute freeze-dried PTH composition (Br. at 42-43), *e.g.*, "the teaching in Holthuis that its preparation should be reconstituted with sterile water." Br. at 42 (emphasis added). However, "a prior art reference is relevant for all that it teaches to those of ordinary skill in the art," *In re Fritch*, 972 F.2d 1260, 1264 (Fed. Cir. 1992), and "is not limited to its specific embodiments," *In re Bode*, 550 F.2d 656, 661 (CCPA 1977) (citations omitted); *see also Young*, 927 F.2d at 591 ("Patents are part of the literature of the art and are relevant for all they contain."). As the Board found, the teachings of the prior art suggest and even recommend the addition of salt water (or salt) to PTH compositions, *e.g.*, Holthuis expressly states that salt water is commonly used to reconstitute freeze-dried PTH compositions. A75, col. 1, lines 32-35. Accordingly, Holthuis' express teaching that most PTH compositions are reconstituted by adding salt water (A75, col. 1, lines 32-35), even directing the reader to a specific example of "a human PTH(1-38) preparation reconstituted into a saline vehicle" (A75, col. 1, lines 53-

54), cannot be disregarded. This alone provides ample motivation for one of ordinary skill to add salt water to PTH compositions, including those taught by Holthuis.

Alternatively, Billger argues that motivation is not found because Endo provides "no" or does not provide "any" expectation of success to achieve "a stable, liquid PTH formulation comprising sodium chloride." Br. at 43-45 (emphasis added). However, an obviousness rejection requires only a reasonable expectation of success. *See In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988). Furthermore, Billger's attempt to attack Endo alone is inappropriate because this is an obviousness rejection. *See In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). Endo is not the sole reference relied upon for teaching a "stable, liquid" PTH composition, rather the rejection is based on Holthuis and Endo. Regardless, those of skill in the art had already achieved a "stable, liquid" PTH composition containing salt. A75, col. 1, lines 53-54 ("a human PTH(1-38) preparation reconstituted into a saline vehicle (see Hodsman . . .)"). Thus, Billger's arguments fail to rebut this *prima facie* obviousness case.

a. The Prior Art Does Not "Teach Away" From the Addition of Salt to PTH Compositions

Billger argues that Martindale 1989, which states that "[s]odium chloride solutions should not be used as they often cause precipitation" (A122), "teaches away" from the claimed invention (Br. at 26-27). However, the Board found this outdated version of the reference less relevant than Martindale 1996 (given Billger's filing date of 1999/2000); Martindale 1996 does not include the language relied upon by Billger. A6-7; A138.

In addition, the Board found that Endo contradicts Martindale 1989 by teaching that adding salt to PTH compositions containing mannitol is beneficial. *Id.* Specifically, Endo teaches freeze-dried compositions containing PTH, buffer, salt, mannitol, and preservative (A80, col. 2, lines 23-35), and that water may be used to reconstitute freeze-dried PTH compositions for injection (A80, col. 2, lines 23-24). The addition of water would result in salt water, thus meeting the limitations of claim 1.

Furthermore, the Board agreed with the Examiner that Holthuis advocates reconstituting PTH compositions using salt water. A4; A50. Similarly, another prior art reference, Piazza et al. ("Piazza"), Canadian Application 2,230,929, submitted by Billger during prosecution shows that saline is a commonly used

carrier for PTH compositions. A219; A322-443. Piazza discloses that "[f]ormulations for parenteral administration may contain as excipients sterile water or saline . . ." A350, lines 14-34 (emphasis added).[3] Billger's specification acknowledges the Examiner's finding that whether salt would cause precipitation depends on the amount of salt added which could be readily determined by an artisan, *i.e.*, because claim 1 has no limitation on the salt concentration, an artisan could choose to add very little salt and fall within the limitations of the claim. A157, lines 1-4; A162, lines 26-27; A48-49. Accordingly, the Board correctly determined that the outdated Martindale 1989 was less relevant than the more contemporaneous Martindale 1996 after weighing the teachings of the references. A6-7.

Billger also argues that Holthuis' cite to Martindale 1989 supports their "teaching away" argument (Br. at 8); however, as the Examiner observed, Holthuis also teaches, in the same paragraph as the cite to Martindale 1989, that most freeze-dried PTH compositions are reconstituted using saline and provides a specific example, the Hodsman reference (A50). Hodsman teaches reconstituting a human PTH preparation using saline. A50. Moreover, as the Examiner

---

[3] It is appropriate for the Court to look to this reference for guidance. *See In re Huston*, 308 F.3d 1267, 1280-81 (Fed. Cir. 2002).

explained, Holthuis was clearly citing Martindale 1989 in its discussion of reviewing various PTH formulations. *Id.* It would seem nonsensical for Holthuis to expressly discuss the common usage of salt water, yet contradict this statement with a passing reference to Martindale 1989.

Furthermore, Billger's speculation that the changes from Martindale 1989 to Martindale 1996 "appears" to be merely "wholesale editorial revisions" (Br. at 29-30) or "merely editorial" (Br. at 31), is simply attorney argument that cannot take the place of evidence. *See In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974). In fact, Billger's arguments are based on incorrect factual findings, *e.g.*, Billger argues that "information omitted from Martindale 1996, such as the usefulness of PTH in the treatment of osteoporosis, clearly was not invalid or obsolete at the time." Br. at 31. To the contrary, Martindale 1996 expressly discusses the use of PTH for the treatment of osteoporosis under the "Treatment" section of "Osteoporosis." ADD16-17. Moreover, the preface in both Martindale 1989 and 1996 specifically tells the reader that Martindale provides information on the adverse effects of pharamceutical preparations. *See* ADD5 and ADD15 (under "Pharmacological and Therapeutic Information," information on the adverse

effects and precautions is provided by concise statements).[4] Hence, if the addition of salt to PTH compositions were indeed as adverse as Billger contends, then surely Martindale 1996 would have contained some sort of warning language.

Finally, Billger complains that Martindale 1996 was cited for the first time in the Board decision (Br. at 26 and 31); however, Billger fails to point out that Martindale 1989 was not submitted until after the final rejection (A274) and shortly before Billger filed a notice of appeal to the Board (A290-91). Thus, the Board appropriately relied on Martindale 1996 in response to Billger's after-final submission. Moreover, if Billger wanted the Board to consider new points with respect to Martindale 1996, a request for reconsideration was available. In arguing that the '724 application "teaches away" from the claimed invention, Billger fails to cite this Court's decision in *Young*, 927 F.2d 588, cited by the Board which expressly rejected the same arguments now asserted by Billger. A7. Essentially, *Young* holds that "[w]hen prior art contains apparently conflicting references, the Board must weigh each reference for its power to suggest solutions

---

[4] Billger also refers to *Martindale, The Extra Pharmacopeia*, The Pharmaceutical Press, London, 30th edition, 1993 ("Martindale 1993"). Br. at 29-32; ADD6-11. The Preface of this edition also contains the same language concerning warnings about adverse effects and precautions. ADD9. Importantly, like Martindale 1996, this edition does not contain any warning about using salt with PTH compositions. ADD11.

to an artisan of ordinary skill." *Young*, 927 F.2d at 591. The facts in *Young* are analogous to the facts here. In *Young*, the applicant argued that the Knudsen reference "taught away" from the prior art Carlisle patent because Knudsen "expressly discredits" Carlisle. *Id.* at 590-91. However, the Board found that Knudsen did not convincingly discredit Carlisle due to Knudsen's failure to duplicate the teachings of Carlisle, and thus, Young's evidence of "teaching away" was unpersuasive. *Id.* at 591-92. Here, Billger argues that the '724 application expressly discredits the teachings of Endo. Br. at 18. However, as discussed, similar to *Young*, the Board found the statements in the '724 application unpersuasive because the application failed to follow the teachings of Endo in its attempts to discredit Endo. A7-8.

Specifically, Endo encourages the addition of mannitol and salt to PTH compositions, as required by claim 1, and not the PTH composition containing sucrose and salt tested for "stability" in the '724 application. *Id.* Moreover, the Board's reasoning is further supported by the Examiner who, after "careful examination," found statements in the '724 application attempting to discredit Endo unsupported and contradicted by the application itself. A51-52. Specifically, while the '724 application states that dimers form in compositions containing PTH, sugar and salt (A85), the Examiner found no quantitative data in

the specification supporting this statement and absolutely no teachings on the formation of dimers when the PTH preparation is stored over a few days, either in liquid or freeze-dried form (A52). Furthermore, Example 7 (A92) (summarized in the Table (A96)) – the closest example to the teachings of Endo – shows no loss of PTH over a period of 1 or 3 months. A51-52.

In both *Young* and in this case, the Board established that the claimed inventions were expressly found in the prior art and after weighing the evidence of "teaching away," found such evidence unpersuasive to rebut a *prima facie* obviousness case. *Young* at 591-92; A7-8. This Court in *Young* affirmed the Board's decision (*Young* at 592) because, as here, the Board gave careful consideration to the evidence relied upon by the applicant and provided reasoning why the evidence was unpersuasive (A7-8). Because the Board's factual finding in this case are supported by substantial evidence, the result should be the same as that in *Young*.

b. Billger's Attempts to Individually Attack Endo are Unavailing Because Endo Provides the Basis for an Obviousness Rejection

Billger argues that Endo is limited to stabilizing freeze-dried PTH compositions, and therefore fails to teach that salt could be used to stabilize liquid PTH compositions. Br. at 34-40. However, the rejection of the claim is based on

section 103 obviousness in view of Holthuis and Endo, not section 102 anticipation. A9. Accordingly, "[n]on-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references." *Merck*, 800 F.2d at 1097. In any case, the Board directly addressed and rejected the same arguments that Billger now makes on appeal. A5-6. Specifically, the Board found that while Holthuis and Endo teach freeze-dried PTH compositions, each reference specifically teaches reconstitution of the compositions in liquid before administration, thus, "the combination does teach a stable, liquid pharmaceutical formulation having the recited components." *Id.*

For example, Holthuis alone teaches the claimed invention by expressly teaching that salt water is commonly used to reconstitute freeze-dried PTH compositions. A75, col. 1, lines 32-35; *see also* A75, col. 1, lines 53-54. Moreover, Endo complements Holthuis in teaching the claimed invention because Endo specifically educates one of ordinary skill that adding salt to the compositions taught by Holthuis (A80, col. 1, lines 29-34) is beneficial. Endo even instructs one of skill to use the same ingredients as the PTH compositions taught by Holthuis. Specifically, Endo teaches that water or salt water, buffers, and preservatives may be added to compositions containing PTH, mannitol, and

salt for subsequent freeze-drying. A80, col. 2, lines 23-35. Endo teaches that water can then be used to reconstitute the freeze-dried PTH compositions for injection. A80, col. 2, lines 23-24. Therefore, as taught by the prior art, either when the PTH composition is prepared in liquid form before freeze-drying, or after the composition is freeze-dried and then reconstituted, such a liquid PTH composition would clearly fall within the limitations of claim 1.

Billger also mischaracterizes the references, arguing that Holthuis and Endo "recogniz[ed] the difficulty in preparing stable, liquid formulations of PTH" and therefore the references "focused on creating stable, lyophilized PTH formulations." Br. at 6. No such statement or inference is found in either Holthuis or Endo, and Billger provides no citation to either reference for support. Moreover, as noted by the Examiner, it is surprising that Billger's specification fails to even acknowledge that it was unexpected that Billger's claimed composition, containing both salt and PTH, lacked the undesirable traits supposedly predicted to occur with such a combination. A45. It was not until after the final rejection that Billger amended claim 1 to add the "stable, liquid" limitation in response to the prior art rejections. A44; A268-69.

c. The Addition of the Term "Stable" in the Preamble Does Not Distinguish the Prior Art

Billger added the term "stable" in the preamble[5] after the final rejection in an attempt to distinguish over the prior art.[6] A44; A268-272. During patent examination, claims are given their broadest reasonable interpretation consistent with the specification. *See, e.g., In re Hyatt*, 211 F.3d 1367, 1372 (Fed. Cir. 2000); *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995); *see also Morris*, 127 F.3d at 1055. As this Court explained, "claims are given their broadest reasonable interpretation during examination proceedings, for the simple reason that before a patent is granted the claims are readily amended as part of the examination process." *Burlington Indus. v. Quigg*, 822 F.2d 1581, 1583 (Fed. Cir. 1987). The starting point for claim interpretation is the plain language of the claims. *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

---

[5] We note that Billger and the Board did not raise the issue that the term "stable" was added to the preamble and that there is no language corresponding to "stable" in the body of the claim. Although not all preamble terms are limitations, even if "stable" is a limitation, this term does not distinguish the prior art here.

[6] We observe that this case is analogous to when an applicant attempts to patent the discovery of an allegedly new property of a known composition. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985); *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990); *In re Crish*, 393 F.3d 1253, 1258 (Fed. Cir. 2004). The term "stable" simply sets forth "a property inherent in, an otherwise old composition" and does not "differentiate the claimed composition from those known to the prior art." *Pearson*, 494 F.2d at 1403.

The claim contains no time limitation associated with the word "stable" (A67; A51), nor is the term "stable" expressly defined in the specification (A5-6; A44-45; A51). The Board observed that although Billger's specification shows examples of "stability" testing of PTH compositions starting at month "zero" (A5-6), no minimum time is specified for determining stability. Billger's own explanation of the term "stable" also failed to provide a time limitation. Specifically, as Billger explained in its reply brief to the Board, the "skilled person would readily understand 'stable,' in the context of a therapeutic formulation, to mean that the environment of the protein or drug, prevents the protein or drug from, for example, precipitating, degrading, or losing activity." A64. Put more simply, does "stable" mean 1 hour, 1 day, 1 week, or even 1 month? Or put another way, if this claim issued as a patent, how long would a PTH composition have to be "stable" to infringe? Logically, the Board found that "stable" compositions would encompass a liquid composition stored for over several days, as taught by Holthuis. A5-6.

Without directly challenging this claim interpretation, Billger appears to argue that the composition must remain "stable" for weeks, even months. *See, e.g.*, Br. at 6 (alleging, without analysis, that "a commercial embodiment of the invention, a stable, liquid PTH formulation is provided from which multiple doses

can be self-administered over a period of 1 to 2 weeks"). Billger's evidence that the claimed composition is "stable" in order to distinguish over the prior art is unconvincing given there is no "stability" data concerning the claimed composition found in the specification. As discussed, every example set forth in the specification is missing at least one claim element. *See* A163-72. Moreover, there seems little doubt that if a party were to either prepare a PTH composition as a liquid for subsequent freeze-drying, or reconstitute a freeze-dried PTH composition for use that same day, Billger would argue that such a liquid composition infringes the limitations of claim 1.

Billger also argues that Endo and Holthuis do not discuss the stability of liquid PTH compositions (Br. at 8); however, not only does Holthuis teach that "mannitol itself confers some stability to the PTH in solution (A76, col. 3, lines 46-47 (emphasis added)), but Billger never provided any evidence that the compositions disclosed in Endo and Holthuis are not "stable" as defined by the Board. Attorney argument cannot take the place of evidence, *Pearson*, 494 F.2d at 1405, especially "when the prior art evidence reasonably allows the PTO to conclude that a claimed feature is present in the prior art, the evidence 'compels such a conclusion if the applicant produces no evidence or argument to rebut it.'" *Crish*, 393 F.3d at 1259-60 (citing *Spada*, 911 F.2d at 708, n.3). Moreover, since

neither Endo nor Holthuis indicates that its PTH compositions are not "stable," there is no reason to believe that one of ordinary skill would conclude that those compositions are not stable.

Because the prior art teaches the stability of the claimed composition for multi-dose usage over several days, the Board's interpretation of the claim term "stable" was reasonable, particularly because Billger has never expressly disputed the Board's claim interpretation, the claim provides no time limitation, and the sparse data found in Billger's specification fails to show that the claimed composition is "stable" to the degree desired by Billger.

VI. CONCLUSION

"Stable, liquid" PTH compositions containing salt were well known in the art. Thus, substantial evidence supports the Board's findings underlying the conclusion that the rejected claims would have been obvious under 35 U.S.C. § 103. Therefore, this Court should affirm that decision.

Respectfully submitted,

John M. Whealan
Solicitor

Heather F. Auyang
Linda Moncys Isacson
Associate Solicitors

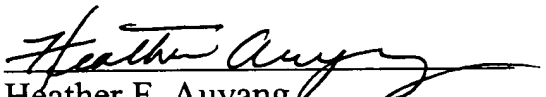
P.O. Box 15667
Arlington, VA 22215
(571) 272-9035

Attorneys for the Director of the United States Patent and Trademark Office

May 11, 2005

RULE 32(a)(7)(c) CERTIFICATE OF COMPLIANCE

I, Heather F. Auyang, Associate Solicitor and an attorney of record for the Appellee Director of the United States Patent and Trademark Office, do hereby certify pursuant to FRAP 32(a)(7) that the foregoing brief complies with the type-volume limitation. The total number of words in the foregoing brief, excluding the table of contents and table of authorities, is 6589, as calculated by the WordPerfect 11.0 program.



Heather F. Auyang
Associate Solicitor

ADDENDUM

MARTINDALE

The Extra Pharmacopoeia

Twenty-ninth Edition

Edited by James E. F. Reynolds

Deputy Editor
Kathleen Parfitt

Assistant Editors
Anne V. Parsons
Sean C. Sweetman

Published by direction of the Council of the Royal Pharmaceutical Society of Great Britain and prepared in the Society's Department of Pharmaceutical Sciences

London
THE PHARMACEUTICAL PRESS
1989

 Published by The Pharmaceutical Press, 1 Lambeth High Street, London SE1 7JN, England.

The first edition of the Extra Pharmacopoeia was published in July 1883. Squire's Companion was incorporated in the twenty-third edition in 1952. The twenty-eighth edition was published in December 1982. This current (twenty-ninth) edition was published in January 1989.

BRITISH LIBRARY CATALOGUING-IN-PUBLICATION DATA

The Extra pharmacopoeia.-29th ed.
1. Drugs. British pharmacopoeias.
I. Title.
615'.11'41

International Standard Book Number (ISBN): 0 85369 210 6. International Standard Serial Number (ISSN): 0263-5364.

Computer composition by Peter Peregrinus Ltd., Hitchin, Hertfordshire; phototypesetting output by Unwin Brothers Ltd., Old Woking, Surrey. Printed and bound in England by The Bath Press, Bath, Avon.

Preface

This edition of Martindale continues the tradition of its predecessors in aiming to provide unbiased concise reports on the actions and uses of most of the world's drugs and medicines to aid the practising pharmacist and physician. While the overall format of this edition remains similar to that of the 28th edition, its contents are the result of a complete revision and the changes resulting from that revision have been considerable.

Monographs have been reorganised into chapters that more accurately reflect current therapeutic practice and the needs of today's reader. The 105 chapters of the last edition have been reorganised into 72 mainly new or renamed chapters. Details have been provided on about 900 new compounds, mostly in the form of new monographs. Over 500 monographs have been deleted where they described substances for which there is little evidence of continued use or interest. Almost 500 other monographs have been deleted where the information could be better incorporated in monographs for related compounds; information on the substances that were the subjects of these deleted monographs can still be traced through the index. The overall effect has been an increase in the coverage of drugs in Martindale, but with a considerable saving of space that has allowed us to make some typographical improvements to assist the reader in locating sections of a monograph.

Abstracts of the relevant aspects of important or useful papers and other publications are still included, but we have written many more referenced reviews of important or contentious topics to back up our editorial text. We have also continued to increase the coverage of proprietary names. More manufacturers are identified for the proprietary names that are included, the directory of manufacturers having increased by 50%. We have also started to include the proprietary names for preparations containing more than one active ingredient and our coverage now extends to many of the English speaking countries.

Considerable changes have been made to Martindale the better to reflect developments in therapeutics in the last 5 or 6 years. Some of the developments have been successful, some have still to produce worthwhile results or remain to be evaluated. A distressing and dominant theme throughout much of the period of revision has been the continuing search for an effective treatment of AIDS. The much enlarged chapter on antiviral agents illustrates some of this work, but it also shows the improvements that there have been in the treatment of other viral diseases. A more optimistic theme has been the expected and growing yield of products from genetic engineering techniques.

A considerable proportion of Martindale is taken up with drugs used to treat infections. Notable features, in addition to developments in antiviral therapy, include the emergence of the fluorinated quinolones and imipenem in the treatment of bacterial infections; the establishment of praziquantel in the treatment of schistosomiasis and other fluke infections; the consolidation of metronidazole and the re-emergence of pentamidine in protozoal infections; and the emergence of the anthelmintic ivermectin for the treatment of onchocerciasis, commendably provided free of charge through a WHO scheme. The increase in cephalosporins seems to continue inexorably.

Advances in the cardiovascular group of drugs have been wide ranging and encouraging. This edition shows the greater benefit that can now be obtained with thrombolytic, anticoagulant, antiplatelet, and haemostatic therapy. ACE inhibitors have established themselves in the treatment of hypertension. Calcium channel blockers continue to appear and offer a range of cardiovascular activity. Improvements have also taken place in lipid regulation.

Developments have continued in the field of peptic ulcer therapy. There are more histamine H2 antagonists, but there is also increased interest in tripotassium dicitratobismuthate in the light of the involvement of *Campylobacter pylori*. Work still progresses on the use of prostaglandins in peptic ulcer and there are new approaches to treatment as with the proton pump inhibitor, omeprazole.

There are other areas where advances are less dramatic, as for instance with antineoplastic agents or antiparkinsonian drugs. Resistance is a continuing concern with antimalarial compounds. Some chapters indicate a decrease in the use of drugs such as the anxiolytic sedatives and hypnotics. A number of nonsteroidal anti-inflammatory drugs have been withdrawn, but our files show that many more are being considered at development stages. Some general anaesthetics have been withdrawn because of toxicity associated with the solvent or vehicle, emphasising the often unregarded importance of formulation in therapeutics.

Martindale is based on published information. It is not a book of standards. Inclusion of a substance or a preparation is not to be considered as a recommendation for use, nor does it confer any status on the substance or preparation. While considerable efforts have been made to check the material in Martindale, the publisher cannot accept any responsibility for errors and omissions. Also the reader is assumed to possess the necessary knowledge to interpret the information that Martindale provides.

Arrangement

PART 1 (pages 1–1535) contains monographs on about 4000 substances arranged in 72 chapters. These chapters generally bring together drugs that have similar uses or actions. Cross-references are used to guide the reader to drugs that may be of interest in related chapters. Most chapters now have an introduction which provides background information on that group of drugs. Some drugs such as the corticosteroids can be considered readily as a group with its members having many common actions; in such cases the introduction provides much of the information for that chapter.

PART 2 (pages 1537–1631) consists of a series of short monographs on some 800 drugs and ancillary substances arranged in the alphabetical order of their main titles. It includes monographs on new drugs, on drugs under investigation, on drugs not easily classified, and on obsolescent drugs still of interest. There are also some monographs on toxic substances, the effects of which may require drug therapy.

PART 3 (pages 1633–43) gives the composition of some 670 proprietary medicines that are advertised to the public in Great Britain and that are usually supplied on demand. The formulas are generally as described by the manufacturers. Herbal medicines have been omitted. This list should not be considered to be comprehensive; some such proprietary medicines are included in Parts 1 and 2, usually if the preparation contains one active ingredient or if proprietary names for similar preparations from other countries are already listed under the monographs. As

in earlier editions of Martindale, the claims made for these products and their recommended doses are not included.

The number of 'counter' proprietary medicines continues to decline.

Indexes

DIRECTORY OF MANUFACTURERS. Throughout the text the names of manufacturers and distributors are abbreviated. Their full names are given in this directory together with the full address if it is available. This directory has considerably increased from about 3000 entries to 4600.

INDEX TO CLINICAL USES. This index is a guide to the uses described in the text; it should not be used otherwise and is not a comprehensive therapeutic index. It refers the reader to the chapters and monographs where the listed diseases are mentioned. The drugs under each disease heading are listed in alphabetical order and not in order of preference.

INDEX TO MARTINDALE IDENTITY NUMBERS. Each monograph in Martindale has an identity number which is used in our computer manipulation. These identity numbers are referred to in the databank (Martindale Online) and will mainly be of value to the user of the online service; however, they may also be of some value to the user of the book. The numbers have no structure and are not significant in themselves. The index lists the identity number followed by the relevant monograph title and the page on which it appears. Identity numbers for chapter introductions have also been included.

GENERAL INDEX. To make fullest use of the contents of Martindale the general index should always be consulted. The exhaustive index to the drugs, preparations, compounds, and pharmacological and therapeutic groups in the book has been compiled to exacting standards and this has resulted in an index of about 62 000 entries. As in previous editions, the index is arranged alphabetically 'word-by-word' rather than 'letter-by-letter'.

Nomenclature

MARTINDALE IDENTITY NUMBERS. Each monograph begins with an identity number which consists of a maximum of 6 figures followed by a check character. These numbers are used in our computer manipulation and their sole purpose is to identify monographs in Martindale. They are referred to in the databank and will mainly be of value to the user of the online or compact disc services; however, they may also be of value to the reader of the book.

TITLES AND SYNONYMS. The title of each monograph is in English, with preference being given to British Approved Names, United States Adopted Names, and International Nonproprietary Names. These 3 authorities are now shown where appropriate against our titles or synonyms. Names given as synonyms include commonly used abbreviated names; English, American, and Latin synonyms; names used in other languages when these may not be readily identifiable; manufacturers' code numbers; and chemical names. In some approved names it is now general policy to use 'f' for 'ph' in sulpha, 't' for 'th', and 'i' for 'y'; for this reason entries in alphabetical lists and indexes should be sought in alternative spellings if the expected spellings are not found. A table of contracted names for ions and groups used in approved names and titles is given on page xx.

CAS REGISTRY NUMBERS. Chemical Abstracts Service (CAS) registry numbers are provided, where available, for each monograph substance to help readers refer to other information systems. Numbers for various forms of the monograph substance are listed with the variation in form given in parenthesis.

Pharmacopoeias

The pharmacopoeias in which each substance appears are listed. Current copies of the pharmacopoeias and their addenda should be consulted for confirmation and for details of standards.

The pharmacopoeias covered include: Argentine, *Austrian*, *Belgian*, Brazilian, *British*, *British Veterinary*, *Chinese*, *Czechoslovakian*; *Egyptian*, *European*, *French*, *German*, Hungarian, *Indian*, *International*, *Italian*, *Japanese*, *Jugoslavian*, Mexican, *Netherlands*, Nordic, Polish, Portuguese, Roumanian, Russian, Spanish, *Swiss*, Turkish, and *United States* (including the *Formulary*). Those *italicised* in the above list either appeared as new editions or were revised by supplements since the last edition of Martindale, and have been examined for this 29th edition.

The abbreviations for these pharmacopoeias are included in the list of abbreviations used in Martindale, see page xvi which also includes details of the edition and/or supplement(s) consulted.

Atomic and Molecular Weights

Atomic weights are based on the table of Atomic Weights as revised in 1983 by the Commission on Atomic Weights and Isotopic Abundance, International Union of Pure and Applied Chemistry and based on the ^{12}C scale (see page xxx). Molecular weights are given corrected to one place of decimals or to four significant figures for relative weights of less than 100.

Pharmaceutical Information

Information on the chemical and physical properties of each substance is given where available and where it is likely to be of use or interest. Compared with earlier editions, this information has been much reduced and included only when it is certain that it applies to the form of substance being described in the monograph. Discrepancies in properties as described in the *B.P.* and *U.S.P.* are indicated.

PERCENTAGE STRENGTHS. Unless otherwise stated, solutions of solids in liquids are expressed as percentage w/v, of liquids in liquids as percentage v/v, and of gases in liquids as percentage w/w.

SOLUBILITY. The figures given for solubility in each monograph have generally been obtained from the major pharmacopoeias in which the substance is described, but should not be considered absolute. Unless otherwise indicated in the text, the figures are for solubility at 'ordinary room temperature' which is considered to be about 20°. Where solubilities are given in words, the following terms describe the indicated solubility ranges:

solubility	
very soluble	1 in less than 1
freely soluble	1 in 1 to 1 in 10
soluble	1 in 10 to 1 in 30
sparingly soluble	1 in 30 to 1 in 100
slightly soluble	1 in 100 to 1 in 1000
very slightly soluble	1 in 1000 to 1 in 10 000
practically insoluble	1 in more than 10 000

STORAGE. Substances and preparations should be stored under conditions which prevent contamination and diminish deterioration.

and the conditions of storage given in the text indicate the precautions recommended in specific cases. Where authorities differ, we have included the most stringent storage requirement. The term 'a cool place' is generally used to describe a place in which the temperature does not exceed 15°. Unless otherwise specified, all injections should be stored in alkali-free containers.

TEMPERATURE. Temperatures are expressed in degrees Celsius (centigrade) unless otherwise indicated.

Pharmacological and Therapeutic Information

Information on the adverse effects, treatment of adverse effects, precautions, absorption and fate, and uses and administration of each substance is provided by concise statements and these are elaborated and expanded by referenced reviews and abstracts from papers and other publications.

This edition contains about 35 500 abstracts or reviews based on information in an ever widening range of publications. In making our selection, we have tried to include the key papers. Where there has been a large body of work, abstracts of some typical papers have been provided with perhaps a selection of references. However, room has also been made for the interesting letter or case report where it is felt that information on a rare effect or action may be useful to the reader.

Much information has been found in sources such as World Health Organization publications, government reports and legislation, and other official and standard publications. Manufacturers' literature has been considered in the light of other available information.

The risks of administering drugs in pregnancy are well known and the general principle is to give a drug only when the benefit to the individual mother outweighs the risk to the foetus. Where there is a clear risk it is noted under the Precautions or Adverse Effects heading but safety should not be inferred from the absence of a statement for any drug.

Interactions are described under the Precautions heading with detailed information being provided in the monograph for the drug that is being affected.

Doses

Doses are described under the Uses and Administration heading with as much detail as is necessary and available. Unless otherwise stated the doses represent the average range of quantities which are generally regarded as suitable for adults when administered by mouth. More information on doses and drug administration may be given in the abstracts and under the Preparations sections. Unless otherwise specified, glucose injection is 5% w/v, sodium chloride injection is 0.9% w/v, and water is purified water.

When doses for children are expressed as a range of quantities within specified age limits, the lower dose applies at the lower age and the higher dose at the higher age.

Formulas

Official preparations are included from current editions of the *British Pharmacopoeia* and the *United States Pharmacopoeia* and *National Formulary*. Preparations from the *British Pharmaceutical Codex 1973* are included if still relevant and not covered by the *British Pharmacopoeia*. Preparations have also been included from the *Australian Pharmaceutical Formulary and Handbook*. The synonyms sometimes included for these preparations may be official synonyms or synonyms that are or have been in common use.

Proprietary Preparations

In Parts 1 and 2, the information on proprietary preparations available in the *UK* is presented with each product being described in the proprietary preparations section of the monograph on its principal ingredient.

Lists of the proprietary names of single-ingredient preparations have been provided for a range of countries including the *UK*. Proprietary names of multi-ingredient preparations have also been included for some countries under the monograph for each of the significant active ingredients. Minor ingredients have not been included.

Readers should be aware that these lists are provided for the purposes of identification. They thus include the names of discontinued preparations as well as names for products registered but still to be marketed.

Acknowledgements

The Editor gratefully acknowledges the advice and assistance of the many experts who have suggested amendments to the text of Martindale. Special thanks are due to Heather M. Ellison, Margaret J. Gilmour, and P. Rowe for reading and commenting on drafts of this edition.

The Editor is grateful to the many organisations that have helped in providing information, including the British Pharmacopoeia Commission, the Medicines Division of the *UK* Department of Health, and the World Health Organization.

Martindale staff have been able to call freely on the expertise of other members of the Royal Pharmaceutical Society's staff. In particular the Editor is grateful to A. Wade, the General Editor, Anne B. Prasad and the editorial staff of the British National Formulary, and Pamela M. North and the staff of the library and information department.

Juliet Kahofer and Gail Neathercoat were assigned to work temporarily on Martindale and their efforts were invaluable. Thanks are also due to Janet M. Batson, P. Gotecha, Chloe Loewe and D. Sheaton, who assisted for some of the period of revision, and to B. J. Yates the Society's publisher. Once again B. Terry of Peter Peregrinus Ltd helped with some of the computer processing and this is gratefully acknowledged.

The contents of this 29th Edition were planned, written, checked, indexed, keyed, and proofed by the Martindale staff. It could not have been produced without that staff's commitment. The Editor welcomes this opportunity to record his gratitude and appreciation of the dedicated services of the clerical staff, Jacqueline O. Baines and Doris D. Moore, and of the editorial staff: Eileen J. Aitchison, P. S. Blake, A. O. Deason, Kathleen Eager, Wendy M. Fareaden, Anne M. P. Gilchrist, Ann Harris, Susan L. Jefferson, Julie M. McCracken, Rosalind McLarney, and J. Martin. Finally, the Editor is indebted to the Assistant Editors, Anne V. Parsons and S. C. Sweetman, and especially the Deputy Editor, Kathleen Parfitt, for invaluable assistance and support.

London
October 1988

MARTINDALE

The Extra Pharmacopoeia

Thirtieth Edition

Edited by James E. F. Reynolds

Deputy Editor
Kathleen Parfitt

Assistant Editors
Anne V. Parsons
Sean C. Sweetman

Published by direction of the Council of the Royal Pharmaceutical Society of Great Britain and prepared in the Society's Department of Pharmaceutical Sciences

London
THE PHARMACEUTICAL PRESS
1993

 Published by The Pharmaceutical Press, 1 Lambeth High Street, London SE1 7JN, England.

The first edition of the Extra Pharmacopoeia was published in July 1883. Squire's Companion was incorporated in the twenty-third edition in 1952. The twenty-ninth edition was published in January 1989. This current (thirtieth) edition was published in April 1993 and reprinted in September 1993

BRITISH LIBRARY CATALOGUING-IN-PUBLICATION DATA

Martindale, William
Extra Pharmacopoeia. - 30Rev. ed
I. Title II. Reynolds, James E.F.
615.1141

International Standard Book Number (ISBN): 0 85369 300 5. International Standard Serial Number (ISSN): 0263-5364.

Computer disks output by Tradespools, Frome, Somerset. Printed and bound in England by The Bath Press, Bath, Avon.

Preface

Over the last 110 years the Extra Pharmacopoeia has developed through 30 editions from William Martindale's small pocketbook to this large volume. While the format has changed, the aim of what is now often known just as Martindale remains one of providing practising pharmacists and physicians with concise unbiased information on the substances used in medicine and pharmacy.

Successive early editions produced by William Martindale established the Extra Pharmacopoeia as a valuable and authoritative source of drug information. The book retained its clinical emphasis through the contributions of W. Wynn Westcott and its chemical and analytical content was developed especially under the editorship of Martindale's son, William Harrison Martindale. The Extra Pharmacopoeia continued to evolve after W.H. Martindale's death until the 25th edition, when it was subjected to a radical reshaping that increased its international coverage, removed the chemical and analytical data, and brought the book back to its early pharmaceutical and clinical roots.

That 25th edition provided a base from which the following 4 editions of Martindale evolved. However, with this 30th edition Martindale has been markedly changed yet again in order to meet the requirements of today's readership. These changes include a massive increase in information on proprietary medicines, a significant shift to a more clinical emphasis, an increase in the number of referenced reviews, and a shortening of the usual period between editions.

As with previous editions the monographs for all the drugs and substances in Martindale have been completely revised. In all there are 5132 monographs describing individual compounds or groups of related compounds. About 280 monographs were deleted from the last edition and about 620 have been added. The majority of the monographs have been grouped into 69 chapters that reflect the compounds' clinical or pharmaceutical use; this forms Part 1 of Martindale. Part 2 contains 832 monographs on drugs that do not readily fit into the chapters of Part 1, on some drugs under investigation, and on nondrug substances of interest to pharmacy and medicine.

The most obvious consequence of the changes that have been made for this edition is the increase in Martindale's size. This edition is 467 pages bigger than its predecessor and all of that increase is due to the enlarged and improved international coverage of proprietary medicines. Martindale is widely used to identify proprietary preparations. In the last edition a start was made to cover preparations containing more than one active ingredient and their proprietary names were listed under each monograph describing the relevant active ingredient. For this edition the coverage of mixed preparations has been widened and the information on each preparation has been presented in such a way that a reader can see at a glance what each contains. Lists of proprietary names still follow each monograph but details of each preparation are now included in a new Part 3 which extends to 481 pages and describes 46 000 preparations or groups of preparations from 14 countries including the *UK* and other European countries, North America, Australia, and South Africa; some preparations from Japan are also included. In addition Part 3 contains entries for official preparations from the *UK* and *USA*. For the proprietary preparations each entry provides the proprietary name, the manufacturer or distributor, the active ingredients, and a summary of that preparation's indications. The quantity of each active ingredient has not been included and dosage forms are only mentioned if different forms have the same proprietary name but different active ingredients. The inclusion of such information would have increased the number of entries inordinately. Also as Part 3 is intended to be used to identify preparations, usually from another country, such details would not necessarily be required for, if an alternative domestic preparation had to be supplied, the dose should be appropriate for that preparation and that patient.

Another development in this edition of Martindale is its increased clinical emphasis. Martindale is still a book of drug monographs but where possible the overall drug treatment of a particular condition has bee drawn together and presented in one major referenced review or discu sion. For example, the different treatments of migraine are reviewed c page 412 and cross-references to that review have been included in th monographs for the drugs discussed. This is something that will be deve oped in future editions.

The inclusion of references from major journals and other publicatior has been a feature of Martindale since its first edition. Useful data ha been extracted from those publications and presented as individual ab stracts. For some important topics in the 29th edition referenced review replaced what would normally have been series of individual abstract That practice has been considerably extended for this edition and whe ever possible balanced reviews of the main publications have been wri ten for the different topics described under each monograph. In all ther are 11 300 reviews and abstracts and the total number of citations i 28 400.

A reference book like Martindale requires a comprehensive index. Th index for this edition has been made up from 153 500 entries. It lists ever drug name, synonym, code, chemical name, and preparation name or title Where a substance is listed as an ingredient of one or more preparation in Part 3, the index entry for that substance is followed by a list of all it preparations. Diseases and conditions requiring treatment have also bee indexed with page references to the major drugs used or to where treat ment has been reviewed in detail. To help the reader locate the indexe information each index entry contains the relevant column number a well as the page number. The importance attached to the index is reflecte in it occupying about one-sixth of the total number of pages of this edi tion.

The general plan since the 25th edition has been to produce a new an completely revised edition of Martindale about every 5 years. Sometime the interval between editions has been longer, but not until this edition ha that interval been reduced significantly. Thanks to the experience of th editorial staff and to modern technology this much enlarged 30th editio is published just over 4 years after the 29th edition to help satisfy the nee for up-to-date information.

Martindale is based on published information. It is not a book of stand ards. Inclusion of a substance or a preparation is not to be considered a a recommendation for use, nor does it confer any status on the substanc or preparation. Many of the monographs in Martindale are a page or mor in length. Summaries have therefore been added to such monographs t provide readers with a brief overview. The inclusion of a summary doe not mean that the drug being described is more important or more effec tive than one without a summary; all it means is that more words were re quired to describe its actions and uses. While considerable efforts have been made to check the material in Martindale, the publisher cannot ac cept any responsibility for errors and omissions. Also the reader is as sumed to possess the necessary knowledge to interpret the information that Martindale provides.

Arrangement

PART 1 (pages 1–1327) contains 4300 monographs arranged in 69 chapters. These chapters generally bring together monographs on drugs and groups of drugs that have similar uses or actions. Cross-references are used to guide the reader to drugs that may be of interest in related chapters. Most chapters have an introduction which provides background information on that group of drugs. Some drugs such as the corticosteroids can be considered readily as a group with its members having many common actions; in such cases the introduction provides much of the information for that chapter. In chapters such as Antibacterial Agents or Antineoplastic Agents and Immunosuppressants the treatment of infections or malignant diseases, respectively, is discussed in detail in the introduction and information on the choice of drug(s) is given there.

PART 2 (pages 1329–1428) consists of a series of 832 short monographs arranged in the alphabetical order of their main titles. It includes monographs on some new drugs, on drugs not easily classified, and on drugs no longer used clinically but still of interest. There are also some monographs on toxic substances, the effects of which may require drug therapy.

PART 3 (pages 1429–1909) contains proprietary preparations from a range of countries as well as official preparations from the *UK* and *USA* from current editions of the *British Pharmacopoeia* and the *United States Pharmacopoeia* and *National Formulary*. Preparations from the *British Pharmaceutical Codex 1973* and earlier editions of the *British Pharmacopoeia* are included if still relevant and not covered by the current *British Pharmacopoeia*. The synonyms sometimes included for these preparations may be official synonyms or synonyms that are or have been in common use. For the proprietary preparations, the information provided includes the proprietary name, the manufacturer or distributor, the active ingredients, and a summary of the indications as given by the manufacturer.

Indexes

DIRECTORY OF MANUFACTURERS. In Martindale the names of manufacturers and distributors are abbreviated. Their full names are given in this directory together with the full address if it is available. This directory contains some 3500 entries.

GENERAL INDEX. To make fullest use of the contents of Martindale, the general index should always be consulted. The exhaustive index to the drugs, preparations, compounds, pharmacological and therapeutic groups, and clinical uses in the book has been prepared from 153 500 individual index entries. As in previous editions, the index is arranged alphabetically 'word-by-word' rather than 'letter-by-letter'. The index indicates the column in which the relevant entry appears as well as the page.

Nomenclature

MARTINDALE IDENTITY NUMBERS. Each monograph title is followed by an identity number in brackets which consists of a maximum of 6 figures followed by a check character. These numbers are used in our computer manipulation and their purpose is to identify monographs in Martindale.

TITLES AND SYNONYMS. The title of each monograph is in English, with preference being given to British Approved Names, United States Adopted Names, and International Nonproprietary Names. These 3 authorities are now shown where appropriate. Names given as synonyms include commonly used abbreviated names; English, American, and Latin synonyms; names used in other languages when these may not be readily identifiable; manufacturers' code numbers; and chemical names. In some approved names it is now general policy to use 'f' for 'ph' in sulpha, 't' for 'th', and 'i' for 'y'; for this reason entries in alphabetical lists and indexes should be sought in alternative spellings if the expected spellings are not found. A table of contracted names for ions and groups used in approved names and titles is given on page xx.

CAS REGISTRY NUMBERS. Chemical Abstracts Service (CAS) registry numbers are provided, where available, for each monograph substance to help readers refer to other information systems. Numbers for various forms of the monograph substance are listed with the variation in form given in parenthesis.

Pharmacopoeias

The selected pharmacopoeias in which each substance appears are listed. Current copies of the pharmacopoeias and their addenda should be consulted for confirmation and for details of standards.

The pharmacopoeias covered include: Austrian, *Belgian*, Brazilian, *British*, *British Veterinary*, Chinese, Czechoslovakian, Egyptian, *European*, *French*, *German*, *Greek*, *Hungarian*, Indian, International, *Italian*, *Japanese*, *Mexican*, *Netherlands*, Nordic, *Portuguese*, Romanian, Russian, *Swiss*, Turkish, *United States* (including the *Formulary*), and Yugoslavian. Those *italicised* in the above list either appeared as new editions or were revised by supplements since the last edition of Martindale, and have been examined for this 30th edition.

The abbreviations for these pharmacopoeias are included in the list of abbreviations used in Martindale, see page xvi which also includes details of the edition and/or supplement(s) consulted.

Atomic and Molecular Weights

Atomic weights are based on the table of Atomic Weights as revised in 1983 by the Commission on Atomic Weights and Isotopic Abundance, International Union of Pure and Applied Chemistry and based on the ^{12}C scale (see page xxvi). Molecular weights are given corrected to one place of decimals or to four significant figures for relative weights of less than 100.

Pharmaceutical Information

Information on the chemical and physical properties of each substance is given when it is likely to be of use or interest, but only when it is certain that it applies to the form of substance being described in the monograph. Discrepancies in properties as described in the *B.P.* and *U.S.P.* are indicated.

PERCENTAGE STRENGTHS. Unless otherwise stated, solutions of solids in liquids are expressed as percentage w/v, of liquids in liquids as percentage v/v, and of gases in liquids as percentage w/w.

SOLUBILITY. The figures given for solubility in each monograph have generally been obtained from the major pharmacopoeias in which the substance is described, but should not be considered absolute. Unless otherwise indicated in the text, the figures are for solubility at 'ordinary room temperature' which is considered to be about 20°. Where solubilities are given in words, the following terms describe the indicated solubility ranges:

solubility	
very soluble	1 in less than 1
freely soluble	1 in 1 to 1 in 10
soluble	1 in 10 to 1 in 30
sparingly soluble	1 in 30 to 1 in 100
slightly soluble	1 in 100 to 1 in 1000
very slightly soluble	1 in 1000 to 1 in 10 000
practically insoluble	1 in more than 10 000

STORAGE. Substances and preparations should be stored under conditions which prevent contamination and diminish deterioration, and the conditions of storage given in the text indicate the precautions recommended in specific cases. Where authorities differ, we have included the most stringent storage requirement. The term 'a cool place' is generally used to describe a place in which the temperature does not exceed 15°. In general, the storage conditions apply to the monograph substance and not its solutions or preparations. Unless otherwise specified, all injections should be stored in alkali-free containers.

TEMPERATURE. Temperatures are expressed in degrees Celsius (centigrade) unless otherwise indicated.

Pharmacological and Therapeutic Information

Information on the adverse effects, treatment of adverse effects, precautions, absorption and fate, and uses and administration of each substance is provided by concise statements and these may be elaborated and expanded by referenced reviews and abstracts from papers and other publications.

This edition contains about 11 300 abstracts or reviews based on information in an ever widening range of publications. We have tried where possible to review the key papers. However, room has also been made for the interesting letter or case report where it is felt that information on a rare effect or action may be useful to the reader.

Much information has been found in sources such as World Health Organization publications, government reports and legislation, and other official and standard publications. Manufacturers' literature has been considered in the light of other available information.

The risks of administering drugs in pregnancy are well known and the

general principle is to give a drug only when the benefit to the individual mother outweighs the risk to the foetus. Where there is a clear risk it is noted under the Precautions or Adverse Effects heading but safety should not be inferred from the absence of a statement for any drug.

Interactions are described under the Precautions heading with detailed information being provided in the monograph for the drug that is being affected.

Doses

Doses are described under the Uses and Administration heading with as much detail as is necessary and available. Unless otherwise stated the doses represent the average range of quantities which are generally regarded as suitable for adults when administered by mouth. More information on doses and drug administration may be given in the abstracts or reviews. Unless otherwise specified, glucose injection is 5% w/v, sodium chloride injection is 0.9% w/v, and water is purified water.

When doses for children are expressed as a range of quantities within specified age limits, the lower dose applies at the lower age and the higher dose at the higher age.

Acknowledgements

The Editor gratefully acknowledges the advice and assistance of the many experts who have suggested amendments to the text of Martindale. Thanks are due to M.J. Gilmour, M. Hooper, J.R. McKim, and especially to L.E. Ramsay for reading and commenting on drafts of this edition.

The Editor is grateful to the many organisations that have helped in providing information, including the World Health Organization, the British Pharmacopoeia Commission, and John Bell & Croydon.

Martindale staff have been able to call freely on the expertise of other members of the Royal Pharmaceutical Society's staff. In particular the Editor is grateful to A. Wade, the General Editor, A.B. Prasad and the editorial staff of the British National Formulary, and P.M. North and the staff of the library and information department.

Thanks are also due to B.J. Yates the Society's publisher and to J. Martin who assisted for some of the period of revision.

Many of the Martindale staff have worked on more than one edition and the Assistant Editors and Deputy Editor have worked with the Editor for the last 3 editions; that experience and the commitment from them and all the staff explain how we have been able to make the considerable developments with this new edition.

The contents of this 30th Edition were planned, written, checked, indexed, keyed, proofed, and processed by the Martindale staff. The Editor welcomes this opportunity to record his gratitude and appreciation of the dedicated services of the clerical staff, J.O. Byrne and D.D. Moore, and of the editorial staff: E.J. Aitchison, P.S. Blake, K. Eager, W.M. Farenden, S.J. Funnell, S.L. Jefferson, J.M. McGlashan, G.C. Neathercoat, A. O'Rourke, S.J. Qureshi, and K.S. Riley. Finally, the Editor is indebted to the Assistant Editors, A.V. Parsons and S.C. Sweetman, and especially the Deputy Editor, K. Parfitt, for invaluable assistance and support.

London December 1992

ere was a potent renal mechanism not inhibited by pamidronate. These results were confirmed by others.[11,12] Ralston *et al.*[12] speculated that the treatment of choice in patients responding incompletely to pamidronate would be inhibitors of renal parathyroid hormone (PTH) receptors and until these are available calcitonin might be worth trying. Since the onset of action of pamidronate is often delayed for 24 to 48 hours combined therapy with pamidronate and salcatonin has been used and is considered by some workers to be the treatment of choice in severe hypercalcaemia where a rapid but sustained effect is desired.[13,21] In a preliminary study in 5 patients[14] pamidronate in association with plicamycin was found to be rapidly effective against severe hypercalcaemia of malignancy resistant to therapy with corticosteroids plus calcitonin or calcitonin, corticosteroids, or pamidronate alone.

Three bisphosphonates were compared in the treatment of cancer-associated hypercalcaemia[15] and pamidronate was considered to be the treatment of choice. Single intravenous infusions of pamidronate 30 mg or clodronate 600 mg or etidronate 7.5 mg per kg body-weight daily by infusion for 3 consecutive days all reduced serum-calcium concentrations from those achieved by rehydration, but onset of effect was most rapid, more profound 6 days after treatment, and longer in duration with pamidronate. However, Kanis *et al.*[16] commented that clodronate in the recommended dose of 1500 mg over 5 days was as effective as pamidronate in most hypercalcaemic patients: Ralston *et al.*[17] still preferred to use a single intravenous infusion of pamidronate.

Hypercalcaemia not related to malignancy has also responded to pamidronate and there have been individual reports of its successful use in patients with hypercalcaemia due to sarcoidosis,[18] thyrotoxicosis,[19] and immobilisation.[20]

1. Thiébaud D. *et al.* Oral versus intravenous AHP,BP (APD) in the treatment of hypercalcemia of malignancy. *Bone* 1986; 7: 247–53.
2. Steeboom HP. *et al.* Comparison of intravenous (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate and volume repletion in tumour-induced hypercalcaemia. *Lancet* 1983; ii: 239–43.
3. Ralston SH. *et al.* Comparison of aminohydroxypropylidene diphosphonate, mithramycin, and corticosteroids/calcitonin in treatment of cancer-associated hypercalcaemia. *Lancet* 1985; ii: 907–10.
4. Cantwell BMJ, Harris AL. Effect of single high dose infusions of aminohydroxypropylidene diphosphonate on hypercalcaemia caused by cancer. *Br Med J* 1987; 294: 467–9.
5. Morton AR. *et al.* Single dose versus daily intravenous aminohydroxypropylidene biphosphonate (APD) for the hypercalcaemia of malignancy. *Br Med J* 1988; 296: 811–14.
6. Ralston SH, Boyle IT. Treatment of hypercalcaemia of malignancy. *Br Med J* 1988; 296: 1468.
7. Judson I. *et al.* Chronic high-dose pamidronate in refractory malignant hypercalcaemia. *Lancet* 1990; 335: 802.
8. Davis JRE, Heath DA. Comparison of different dose regimes of aminohydroxypropylidene-1,1-bisphosphonate (APD) in hypercalcaemia of malignancy. *Br J Clin Pharmacol* 1989; 28: 269–74.
9. Kanis JA. *et al.* Effects of diphosphonates in hypercalcaemia due to neoplasia. *Lancet* 1986; i: 615–16.
10. Gurney H. *et al.* Renal phosphate threshold and response to pamidronate in humoral hypercalcaemia of malignancy. *Lancet* 1989; ii: 241–4.
11. Beex L. *et al.* Pamidronate and hypercalcaemia of malignancy. *Lancet* 1989; ii: 617.
12. Ralston SH. *et al.* Pamidronate and hypercalcaemia of malignancy. *Lancet* 1989; ii: 617–18.
13. Ralston SH. *et al.* Treatment of cancer associated hypercalcaemia with combined aminohydroxypropylidene diphosphonate and calcitonin. *Br Med J* 1986; 292: 1549–50.
14. Ralston SH. *et al.* Treatment of severe hypercalcaemia with mithramycin and aminohydroxypropylidene bisphosphonate. *Lancet* 1988; ii: 277.
15. Ralston SH. *et al.* Comparison of three intravenous bisphosphonates in cancer-associated hypercalcaemia. *Lancet* 1989; ii: 1180–2.
16. Kanis JA. *et al.* Use of diphosphonates in hypercalcaemia due to malignancy. *Lancet* 1990; 335: 170–1.
17. Ralston SH. *et al.* Use of bisphosphonates in hypercalcaemia due to malignancy. *Lancet* 1990; 335: 737.
18. Gibbs CJ, Peacock M. Hypercalcaemia due to sarcoidosis corrects with bisphosphonate treatment. *Postgrad Med J* 1986; 62: 937–8.
19. Tan TT. *et al.* Treatment of hypercalcaemia in thyrotoxicosis with aminohydroxypropylidene diphosphonate. *Postgrad Med J* 1988; 64: 224–7.
20. Gallacher SJ. *et al.* Immobilization-related hypercalcaemia—a possible novel mechanism and response to pamidronate. *Postgrad Med J* 1990; 66: 918–22.
21. Thiébaud D. *et al.* Fast and effective treatment of malignant hypercalcemia: combination of suppositories of calcitonin and a single infusion of 3-amino 1-hydroxypropylidene-1-bisphosphonate. *Arch Intern Med* 1990; 150: 2125–8.

Osteoporosis. For a brief description of osteoporosis and its treatment, see p.654.

Results of a placebo-controlled study[1] involving 35 patients indicated that pamidronate 150 mg daily by mouth for 1 year together with a daily calcium supplement of 1 g arrested the loss of bone mass in patients on long-term glucocorticoid therapy when compared with controls who only received calcium. Apart from nausea, pamidronate was well-tolerated; there was no evidence of osteomalacia. Continuation of the study for a further year[2] in 13 patients (5 receiving pamidronate; 8 on placebo) suggested that pamidronate has a sustained beneficial effect in steroid osteoporosis.

1. Reid IR. *et al.* Prevention of steroid-induced osteoporosis with (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate (APD). *Lancet* 1988; i: 143–6.
2. Reid IR. *et al.* Two-year follow-up of biphosphonate (APD) treatment in steroid osteoporosis. *Lancet* 1988; ii: 1144.

Paget's disease of bone. For a brief description of Paget's disease of bone and its treatment, see p.654.

Disodium pamidronate has been administered orally or intravenously. In an uncontrolled study patients with Paget's disease generally responded to treatment with pamidronate given by mouth in an average daily dose of 500 mg (range 300 to 800 mg) for minimum periods of 4 to 9 months.[1] Gastric intolerance was not a problem, possibly because the tablets were enteric-coated.

Others have preferred to use the intravenous route to eliminate problems of variable absorption, poor bioavailability, and gastro-intestinal side-effects. In a preliminary open study involving 20 patients with severe symptomatic Paget's disease, Cantrill *et al.*[2] gave pamidronate by intravenous infusion in a dose of 15 mg daily for five consecutive days or weekly for 12 weeks. Both regimens were generally successful and well-tolerated. Harinck *et al.*[3] compared oral and intravenous treatment regimens in 142 patients with active Paget's disease and found no difference in the long term between pamidronate 600 mg daily by mouth continued for 6 months after serum-alkaline phosphatase activity was back to normal or until urinary hydroxyproline excretion was back to normal or pamidronate 20 mg daily by intravenous infusion for 10 days. They considered the intravenous regimen would be preferable in most patients. Daily intravenous infusions might be impractical and Anderson and Cantrill[4] developed a weekly or fortnightly intravenous infusion regimen which they claimed was successful. The regimen starts with a single intravenous infusion of pamidronate 30 mg in 250 mL of saline over 2 hours followed after one week by 60 mg in 500 mL over 4 hours; the 60-mg dose is then repeated at intervals of 14 days depending on the severity of the disease.

A patient with Paget's disease refractory to human calcitonin has been reported[5] to respond to treatment with disodium pamidronate 30 mg in 1000 mL of physiological saline by intravenous infusion over 6 hours on each of 3 consecutive days.

1. Mautalen CA. *et al.* Efficacy of the bisphosphonate APD in the control of Paget's bone disease. *Bone* 1985; 6: 429–32.
2. Cantrill JA. *et al.* Low dose intravenous 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD) for the treatment of Paget's disease of bone. *Ann Rheum Dis* 1986; 45: 1012–18.
3. Harinck HIJ. *et al.* Paget's disease of bone: early and late responses to three different modes of treatment with aminohydroxypropylidene bisphosphonate (APD). *Br Med J* 1987; 295: 1301–5.
4. Anderson DC, Cantrill JC. Treatment of Paget's disease of bone. *Br Med J* 1988; 296: 291.
5. Drake S. *et al.* Pamidronate sodium and calcitonin-resistant Paget's disease: immediate response in a patient. *Arch Intern Med* 1989; 149: 401–3.

Proprietary Names
Aredia, Aredin.
Preparation details are given in Part 3.

Neridronic Acid (4536-s)

Neridronic Acid *(rINN)*.
AHDP; AHHexBP; Aminohexane Diphosphonate. (6-Amino-1-hydroxyhexylidene)diphosphonic acid.
$C_6H_{17}NO_7P_2$ = 277.2.
CAS — 79778-41-9.

Neridronic acid is used as a neridronate salt, a bisphosphonate with the general properties of disodium etidronate. It inhibits bone resorption and has been given by mouth in the treatment of Paget's disease of bone.

References.
1. Delmas PD. *et al.* Beneficial effects of aminohexane diphosphonate in patients with Paget's disease of bone resistant to sodium etidronate. *Am J Med* 1987; 83: 276–82.

Parathyroid Hormone (8051-x)

Parathyrin; PTH.
CAS — 9002-64-6.

Parathyroid hormone is a single-chain polypeptide isolated from the parathyroid glands. It contains 84 amino acids and in man the first 34 appear to be responsible for the hormonal activity. The amino-acid sequence varies according to the source.

Endogenous parathyroid hormone is involved in the maintenance of plasma-calcium concentrations having a hypercalcaemic effect through its actions on bone, kidney, and the gastro-intestinal tract.

Exogenous parathyroid hormone was formerly used to raise the plasma-calcium concentration in acute hypoparathyroidism with tetany. The response to an intravenous injection of parathyroid hormone has also been used in the differential diagnosis of hypoparathyroidism and pseudo-hypoparathyroidism.

Synthetic preparations of the first 34 amino acids of human and bovine parathyroid hormones (PTH 1-34) are now used for diagnostic purposes and are being investigated for the treatment of osteoporosis, see Teriparatide Acetate, below.

Proprietary Names
Parathorm, Para-Thor-Mone.
Multi-ingredient preparations. Neuromade.
Preparation details are given in Part 3.

Teriparatide Acetate (3640-n)

Teriparatide Acetate *(USAN, rINNM)*.
hPTH 1-34 (teriparatide).
$C_{181}H_{291}N_{55}O_{51}S_2.xH_2O.xC_2H_4O_2$.
CAS — 52232-67-4 (teriparatide); 99294-94-7 (teriparatide acetate).

Units

The potency of teriparatide acetate is expressed in terms of units of human parathyroid hormone activity.

The first International Reference Preparation (1981) of parathyroid hormone, human, for immunoassay contains 0.1 unit in approximately 100 ng of freeze-dried purified hormone.

Adverse Effects

Gastro-intestinal disturbances, a metallic taste, tingling of the extremities, and pain at the site of injection have occasionally been associated with the intravenous infusion of teriparatide acetate.

Uses and Administration

Teriparatide is a synthetic polypeptide that consists of the 1-34 amino-acid fragment of human parathyroid hormone, the biologically active *N*-terminal region. The acetate is given by intravenous infusion in the differential diagnosis of hypoparathyroidism and pseudohypoparathyroidism; a dose of 200 units is infused over 10 minutes. A 1-38 amino-acid fragment (hPTH 1-38) has also been used.

Teriparatide acetate has been given by subcutaneous injection in the management of osteoporosis.

Diagnostic use. In hypoparathyroidism, hypocalcaemia and hyperphosphataemia result from a deficiency in endogenous parathyroid hormone, whereas pseudohypoparathyroidism comprises a group of inherited disorders, characterised by resistance to the effects of parathyroid hormone. In pseudohypoparathyroidism type I, patients may be normocalcaemic or hypocalcaemic, and fail to demonstrate a phosphaturic response or increased urinary cyclic AMP following parathyroid hormone administration. In patients with the less common type II form of the disease, the urinary cyclic AMP, but not the phosphaturic, response to exogenous parathyroid hormone is normal.

Teriparatide acetate is used diagnostically to distinguish between hypoparathyroidism and pseudohypoparathyroidism types I and II. In the modified Ellsworth Howard test active urine output is initiated and maintained by drinking water and urinary concentrations of cyclic AMP and phosphate measured at standardised times before and after intravenous infusion of teriparatide acetate; measurements are corrected for creatinine excretion.[1] A synthetic 1-38 fragment of human parathyroid hormone (1-38 hPTH) has also been used diagnostically.[2]

1. Mallette LE. Synthetic human parathyroid hormone 1-34 fragment for diagnostic testing. *Ann Intern Med* 1988; 109: 800–4.
2. Kruse K, Kracht U. A simplified diagnostic test in hypoparathyroidism and pseudohypoparathyroidism type I with synthetic 1-38 fragment of human parathyroid hormone. *Eur J Pediatr* 1987; 146: 373–7.

Osteoporosis. In a study of 21 patients with osteoporosis, the administration of teriparatide as a daily subcutaneous injection for 6 to 24 months produced a substantial increase in iliac trabecular bone volume. Calcium and phosphate balance improved in some patients but there was no significant improvement overall.[1] Slovik *et al.*[2] demonstrated that daily administration of teriparatide by subcutaneous injection supplemented with calcitriol by mouth

MARTINDALE

The Extra Pharmacopoeia

Thirty-first Edition

Edited by James E F Reynolds

Deputy Editor
Kathleen Parfitt

Assistant Editors
Anne V Parsons
Sean C Sweetman

Published by direction of the Council of the Royal Pharmaceutical Society of Great Britain and prepared in the Society's Publications Department

London
ROYAL PHARMACEUTICAL SOCIETY
1996

 Published by the Royal Pharmaceutical Society of Great Britain, 1 Lambeth High Street, London SE1 7JN, England.

The first edition of the Extra Pharmacopoeia was published in July 1883. Squire's Companion was incorporated in the twenty-third edition in 1952. The thirtieth edition was published in April 1993. This (thirty-first) edition was published in April 1996.

International Standard Book Number (ISBN): 0-85369-342-0. International Standard Serial Number (ISSN): 0263-5364.

Typeset from tape by Page Bros, Norwich, Norfolk. Printed by Jarrold Printing, Norwich, Norfolk. Bound by JW Braithwaite and Son Limited, Wolverhampton, West Midlands.

Preface

The aim of Martindale. The Extra Pharmacopoeia is to provide practising pharmacists and physicians with unbiased evaluated information on drugs and medicines used throughout the world. Martindale therefore has to develop if it is to continue to meet that aim since the body of knowledge on existing drugs continues to grow, new drugs still emerge, new preparations are launched, old preparations abandoned, reformulated, or redefined, and the information needs of those practising pharmacy and medicine continue to evolve. The considerable changes that have been made with this edition are intended to meet those needs and we hope that they make the book easier to use.

All the monographs from the last edition have been revised, 173 having been deleted and 283 added, and reorganised into chapters that better reflect the uses of the drugs being described. For example, there is now one large chapter on Cardiovascular Agents rather than several chapters on groups such as Diuretics or Antihypertensive Agents. As a result, this edition contains 54 chapters in Part 1, fifteen fewer than in the 30th edition.

The most significant development, though, with this edition is the inclusion of a description of those diseases that are treated by drugs and a review of the choice of such treatment. Links are provided between the monographs and these reviews and *vice versa*. The reader can easily refer to a monograph from a disease review for further details about that drug. Conversely, reference can be made from a monograph to a disease review to see what other therapy may be used, although within each monograph we have tried to indicate that drug's place in the treatment of a disease or symptom for which it is indicated. This feature of the 31st edition of Martindale completes a development that was started in some chapters of the last edition.

The 30th edition was published 4 years after its predecessor to meet the need for more up-to-date information. That need is even more pressing today, hence the appearance of this edition 3 years after the 30th edition. For those who require even more up-to-date information from Martindale there are the electronic versions, sections of which are updated more frequently.

The information on preparations which is an important feature of Martindale has also been revised and the coverage of countries widened. Part 3 now describes 62 500 preparations or groups of preparations from 17 different countries. Within each preparation entry the individual ingredients have been indexed with the page numbers of the relevant drug monographs. In addition, entries in the General Index for single-ingredient preparations show the page numbers of the preparation entries in Part 3 as well as of the appropriate monographs.

Changes have been made to the typography to improve readability. Clearer headings have been introduced. Readers should welcome the increased type size in some sections as well as the adjustments to spacing which make the pages easier on the eye.

These developments have led to an increase in the size of Parts 1, 2, and 3. To compensate, and to keep the book in one volume, we have refined the index. We hope that the changes and reduction in size will make it easier to use without any loss of access to the edition's contents.

Martindale is based on published information and 26 300 selected references are included. Our aim is to cover the important studies and useful reviews and to place them in context. Mega studies and meta-analyses are playing a growing and important role in the study of drug treatment, and their findings and conclusions are considered in many of our chapters. However, there is also a place for the anecdotal report and the small study, and information from such sources is included where appropriate.

Martindale is not a book of standards. Inclusion of a substance or a preparation is not to be considered as a recommendation for use, nor does it confer any status on the substance or preparation. Many of the monographs in Martindale are a page or more in length. Summaries have therefore been added to such monographs to provide readers with a brief overview. The inclusion of a summary does not mean that the drug being described is more important or more effective than one without a summary; all it means is that more words were required to describe its actions and uses. While considerable efforts have been made to check the material in Martindale, the publisher cannot accept any responsibility for errors and omissions. Also the reader is assumed to possess the necessary knowledge to interpret the information that Martindale provides.

Arrangement

PART 1 (pages 1–1666) contains 4458 monographs arranged in 54 chapters. These chapters generally bring together monographs on drugs and groups of drugs that have similar uses or actions. Those chapters that describe drugs used in the management of disease contain descriptions of those diseases together with reviews of the choice of treatments and cross-references to the drugs discussed.

PART 2 (pages 1667–1768) consists of a series of 784 short monographs arranged in the alphabetical order of their main titles. It includes monographs on some new drugs, on drugs not easily classified, and on drugs no longer used clinically but still of interest. There are also some monographs on substances or techniques that may have a bearing on drug treatment such as bradykinin and gene therapy. Finally there are monographs on toxic substances, the effects of which may require drug therapy.

PART 3 (pages 1769–2395) contains proprietary preparations from a range of countries as well as official preparations from the *UK* and *USA* from current editions of the *British Pharmacopoeia* and the *United States Pharmacopoeia* and *National Formulary*. Preparations from the *British Pharmaceutical Codex 1973* and earlier editions of the *British Pharmacopoeia* are included if still relevant and not covered by the current *British Pharmacopoeia*. The synonyms sometimes included for these preparations may be official synonyms or synonyms that are or have been in common use. For the proprietary preparations, the information provided includes the proprietary name, the manufacturer or distributor, the active ingredients, and a summary of the indications as given by the manufacturer. We had hoped to include some information on those preparations manufactured within the hospital service, often known as 'hospital specials', and we are grateful to those hospitals who sent us data. Unfortunately there were some limitations on the amount of information that could be made public and the project had to be dropped.

Indexes

DIRECTORY OF MANUFACTURERS. In Martindale the names of manufacturers and distributors are abbreviated. Their full names are given in this directory together with the full address if it is available. This directory contains some 4800 entries.

GENERAL INDEX. To make fullest use of the contents of Martindale the general index should always be consulted. The exhaustive index to the drugs, preparations, compounds, pharmacological and therapeutic groups, and clinical uses in the book has been prepared from 131500 individual index entries. As in previous editions, the index is arranged alphabetically 'word-by-word' rather than 'letter-by-letter'. The index indicates the column in which the relevant entry appears as well as the page.

Nomenclature

MARTINDALE IDENTITY NUMBERS. Each monograph title is followed by an identity number in brackets which consists of a maximum of 6 figures followed by a check character. These numbers are used in our computer manipulation and their purpose is to identify monographs in Martindale.

TITLES AND SYNONYMS. The title of each monograph is in English, with preference being given to British Approved Names, United States Adopted Names, and International Nonproprietary Names. These 3 authorities are now shown where appropriate. Names given as synonyms include commonly used abbreviated names; English, American, and Latin

synonyms; names used in other languages when these may not be readily identifiable; manufacturers' code numbers; and chemical names. In some approved names it is now general policy to use 'f' for 'ph' in sulpha, 't' for 'th', and 'i' for 'y'; for this reason entries in alphabetical lists and indexes should be sought in alternative spellings if the expected spellings are not found. A table of contracted names for ions and groups used in approved names and titles is given on page xix.

CAS REGISTRY NUMBERS. Chemical Abstracts Service (CAS) registry numbers are provided, where available, for each monograph substance to help readers refer to other information systems. Numbers for various forms of the monograph substance are listed with the variation in form given in parenthesis.

Pharmacopoeias

The selected pharmacopoeias in which each substance appears are listed. Current copies of the pharmacopoeias and their addenda should be consulted for confirmation and for details of standards.

The pharmacopoeias covered include: *Austrian, Belgian, British, British Veterinary, Chinese, Czechoslovakian, European, French, German,* Hungarian, *International, Italian,* Japanese, *Netherlands, Portuguese, Swiss,* and *United States* (including the *Formulary*). Those *italicised* in the above list either appeared as new editions or were revised by supplements since the last edition of Martindale, and have been examined for this 31st edition.

The abbreviations for these pharmacopoeias are included in the list of abbreviations used in Martindale, see page xv which also includes details of the edition and/or supplement(s) consulted.

The standards of the European Pharmacopoeia take precedence over the standards of the national pharmacopoeias of those countries that are parties to the Convention on the Elaboration of a European Pharmacopoeia. These countries are currently Austria, Belgium, Bosnia-Herzegovina, Croatia, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Slovenia, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the Former Yugoslav Republic of Macedonia.

Atomic and Molecular Weights

Atomic weights are based on the table of Atomic Weights as revised in 1993 by the Commission on Atomic Weights and Isotopic Abundance, International Union of Pure and Applied Chemistry and based on the ^{12}C scale (see page xxi). Molecular weights are given corrected to one place of decimals or to four significant figures for relative weights of less than 100.

Pharmaceutical Information

Information on the chemical and physical properties of each substance is given when it is likely to be of use or interest, but only when it is certain that it applies to the form of substance being described in the monograph. Discrepancies in properties as described in the BP and USP are indicated.

PERCENTAGE STRENGTHS. Unless otherwise stated, solutions of solids in liquids are expressed as percentage w/v, of liquids in liquids as percentage v/v, and of gases in liquids as percentage w/w.

SOLUBILITY. The figures given for solubility in each monograph have generally been obtained from the major pharmacopoeias in which the substance is described, but should not be considered absolute. Unless otherwise indicated in the text, the figures are for solubility at temperatures between 15° and 25°. The information usually relates to w/v solubilities but in some cases is v/v if the monograph substance itself is a liquid. Where solubilities are given in words, the following terms describe the indicated solubility ranges:

solubility	
very soluble	1 in less than 1
freely soluble	1 in 1 to 1 in 10
soluble	1 in 10 to 1 in 30
sparingly soluble	1 in 30 to 1 in 100
slightly soluble	1 in 100 to 1 in 1000
very slightly soluble	1 in 1000 to 1 in 10 000
practically insoluble	1 in more than 10 000

STORAGE. Substances and preparations should be stored under conditions which prevent contamination and diminish deterioration, and the conditions of storage given in the text indicate the precautions recommended in specific cases. Where authorities differ, we have included the most stringent storage requirement. The term 'a cool place' is generally used to describe a place in which the temperature is between 8° and 15°. In general, the storage conditions apply to the monograph substance and not its solutions or preparations.

TEMPERATURE. Temperatures are expressed in degrees Celsius (centigrade) unless otherwise indicated.

Pharmacological and Therapeutic Information

Information on the adverse effects, treatment of adverse effects, precautions, pharmacokinetics, and uses and administration of each substance is provided by concise statements and these may be elaborated and expanded by referenced reviews and abstracts from papers and other publications.

This edition contains about 11 600 abstracts or reviews based on information in an ever widening range of publications. We have tried where possible to review the key papers. However, room has also been made for the interesting letter or case report where it is felt that information on a rare effect or action may be useful to the reader.

Much information has been found in sources such as World Health Organization publications, government reports and legislation, and other official and standard publications. Manufacturers' literature has been considered in the light of other available information.

The risks of administering drugs in pregnancy are well known and the general principle is to give a drug only when the benefit to the individual mother outweighs the risk to the foetus. Where there is a clear risk it is noted under the Precautions or Adverse Effects heading but safety should not be inferred from the absence of a statement for any drug.

Interactions are described under the Precautions heading with detailed information being provided in the monograph for the drug that is being affected.

Doses

Doses are described under the Uses and Administration heading with as much detail as is necessary and available. Unless otherwise stated the doses represent the average range of quantities which are generally regarded as suitable for adults when administered by mouth. More information on doses and drug administration may be given in the abstracts or reviews. Unless otherwise specified, glucose injection is 5% w/v, sodium chloride injection is 0.9% w/v, and water is purified water.

When doses for children are expressed as a range of quantities within specified age limits, the lower dose applies at the lower age and the higher dose at the higher age.

Acknowledgements

The Editor gratefully acknowledges the advice and assistance of the many experts who have suggested amendments to the text of Martindale. Thanks are due to DN Bateman, P Bennett, MJ Brodie, PR Jackson, T Pullar, LE Ramsay, CJC Roberts, M Summerhayes, and WW Yeo for reading and commenting on drafts of this edition.

The Editor is grateful to the many organisations that have helped in providing information, including the World Health Organization and the British Pharmacopoeia Commission.

Martindale staff have been able to call freely on the expertise of other members of the Royal Pharmaceutical Society's staff. In particular the Editor is grateful to A Wade, the General Editor, AB Prasad and the editorial staff of the British National Formulary, and the staff of the library and information department. Thanks are also due to S Dutton and K Rowan.

Almost all of the Martindale staff have worked on more than one edition and many have worked with the Editor for the last 3 or 4 editions; that experience and the commitment from them and all the staff explain how we have once again been able to make the considerable developments to Martindale.

Calcium Regulating Agents

ntroduction

ie endogenous hormones, parathyroid hormone d calcitonin, are involved in the regulation of cal-um homoeostasis.

alcitonins and the bisphosphonates (formerly own as biphosphonates or diphosphonates and ex-mplified by disodium clodronate, etidronate, and midronate) inhibit bone resorption and thus have ypocalcaemic effect. They are therefore used in e treatment of conditions associated with in-eased bone resorption (see below) and in the man-ement of hypercalcaemia, especially that sociated with malignancy (see p.1170). Radioac-ely labelled bisphosphonates are used as bone anning agents.

rathyroid hormone, which has a hypercalcaemic fect, was formerly used in the differential diagno- of hypoparathyroidism and pseudohypoparathy-idism, but has been replaced by teriparatide .782), the synthetic 1-34 amino-acid fragment of man parathyroid hormone.

one and Bone Disease

ie skeleton acts as mechanical support and protec-n to softer tissues and organs. It is also important electrolyte homoeostasis, acting as a reservoir of rtain ions and minerals such as calcium, phospho-s, and magnesium.

one is composed of two elements: an organic ma-x, called **osteoid**, consisting mainly of collagen, d a mineral phase deposited through it comprising out 70% of the skeletal mass, and composed iefly of hydroxyapatite (a complex crystalline salt calcium and phosphate). Two structural forms are own in mature bone, namely cortical (lamellar) ne, which has a dense, continuous structure, and abecular (cancellous) bone, which has 'spongy' ucture of linked plates and is associated with high ne turnover and growth.

one is a dynamic tissue which undergoes continual rmation and resorption. Bone cells originate in the arrow and share common origins with blood cells. one cells include **osteoblasts** that synthesise oste-d and probably promote its subsequent mineralisa-n, and are thus responsible for bone formation; e **osteoclasts** are the principal bone-resorbing lls. The actions of these two types of bone cell are closely linked. Bone also contains a third type of cell, the **osteocytes** which are derived from osteoblasts and are thought to be involved in the movement of minerals. Bone cells are controlled by systemic hormones including parathyroid hormone, 1,25-dihydroxycholecalciferol (calcitriol), and calcitonin and local regulators such as bone morphogenetic proteins and interleukin-1; vitamin K is also thought to play a role, and they are affected by other hormones including corticosteroids and sex hormones.

Bone diseases may be due to defects in the production of osteoid or its mineralisation, or to an imbalance in resorption and formation of bone. Some of the commoner diseases of bone are described below.

Ectopic ossification. Ectopic ossification[1] (heterotopic ossification) is a condition in which mature bone develops in non-skeletal tissues, commonly the connective tissue of muscles. It occurs following trauma, for example after joint dislocation or surgery such as total hip replacement, and also after neurological damage such as severe head or spinal cord injuries. Ectopic bone formation usually starts about 2 weeks after the injury, though symptoms which include localised pain, swelling, and restriction of movement, may not be present for 8 to 10 weeks. A congenital form of ectopic ossification, myositis ossificans progressiva also occurs but is rare.

Ectopic ossification should be distinguished from the calcification of soft tissue which may occur in connective-tissue disorders or in parathyroid disorders due to high circulating concentrations of calcium and/or phosphate.

Treatment of established ectopic bone is limited to surgical resection. Patients at high risk of ectopic bone formation should therefore receive prophylaxis with radiotherapy, physiotherapy, or drug therapy. While prophylaxis does not always prevent the development of ectopic ossification, it can decrease its occurrence and severity. Prophylactic measures should be begun as early as possible and for orthopaedic surgery may be started before the operation. Prophylaxis is also required if mature ectopic bone is to be surgically excised in order to minimise the rate of recurrence. Bisphosphonates such as disodium etidronate which inhibit the mineralisation of the deposited bone have been advocated[2] but they do not prevent the formation of the osteoid matrix. Also when etidronate is discontinued, some mineralisation can occur resulting in delayed ectopic ossification though it is usually less severe. More promising are the nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, or indomethacin; these appear to significantly reduce the incidence of ectopic bone formation,[3,4] possibly by inhibiting the synthesis of osteoactive prostaglandins.

For further information on the agents mentioned above, see Disodium Etidronate, p.779 NSAIDs, p.72

1. Singer BR. Heterotopic ossification. *Br J Hosp Med* 1993; **49**: 247–55.
2. Finerman GAM, Stover SL. Heterotopic ossification following hip replacement or spinal cord injury: two clinical studies with EHDP. *Metab Bone Dis Relat Res* 1981; **4 & 5**: 337–42.
3. Schmidt SA, *et al.* The use of indomethacin to prevent the formation of heterotopic bone after total hip replacement: a randomized, double-blind clinical trial. *J Bone Joint Surg (Am)* 1988; **70A**: 834–8.
4. Pagnani MJ, *et al.* Effect of aspirin on heterotopic ossification after total hip arthroplasty in men who have osteoarthrosis. *J Bone Joint Surg (Am)* 1991; **73A**: 924–9.

Malignant neoplasms of the bone. For the management of malignant neoplasms of the bone, see p.524 and p.534. For a review of hypercalcaemia of malignancy and its management, see p.1170.

Osteogenesis imperfecta. Osteogenesis imperfecta (brittle bone syndrome) is a congenital disorder of connective tissue that occurs with different degrees of severity. Osteoid, the main organic component of the bone matrix, is composed of bundles of collagen, and defective collagen synthesis results in brittle bones which fracture easily; short stature, joint laxity, teeth defects, and hearing abnormalities may also occur.

Orthopaedic treatment and physical activity programmes form the basis of therapy. Beneficial effects have been reported with calcitonins in conjunction with calcium supplements,[1,2] but in general, drug therapy is not considered to be very effective.

For further information on the agents mentioned above, see Calcitonins, p.776 Calcium, p.1176

1. Castells S, *et al.* Therapy of osteogenesis imperfecta with synthetic salmon calcitonin. *J Pediatr* 1979; **95**: 807–11.
2. Rebelo I, *et al.* Effect of synthetic salmon calcitonin therapy in children with osteogenesis imperfecta. *J Int Med Res* 1989; **17**: 401–5.

Osteomalacia. Osteomalacia occurs when there is impaired mineralisation of the bone matrix resulting in 'soft' bones. Patients usually present with bone pain and muscle weakness and may have subclinical fractures. Rickets refers to defective mineralisation of growing bone and is therefore restricted to children; it is associated with retarded growth, skeletal deformities, teeth defects, and muscle hypotonia.

Inadequate bone mineralisation may be caused by vitamin D deficiency or its abnormal metabolism, phosphate depletion, calcium deficiency, or a primary disorder of bone matrix such as hypophosphatasia in which a deficiency of alkaline phosphatase results in an increase in pyrophosphate, an inhibitor of bone mineralisation. Some drugs such as etidronate, or metal ions such as aluminium, can also interfere with bone mineralisation. For osteomalacia associated with chronic renal failure, see Renal Osteodystrophy, p.775.

Several hereditary disorders are associated with the development of rickets including vitamin D-pseudodeficiency rickets (vitamin D-dependent rickets), in which there is impaired synthesis of 1,25-dihydroxycholecalciferol (Type I) or receptor resistance to 1,25-dihydroxycholecalciferol (Type II) and X-linked hypophosphataemic rickets.[1]

Treatment is primarily aimed at correcting any underlying deficiency. Vitamin D substances, calcium, or phosphate supplements can be given by mouth as appropriate but doses require careful individual adjustment to maintain calcium and phosphate concentrations within normal limits. If malabsorption is suspected, larger doses or parenteral administration may be necessary.

Type I vitamin D-pseudodeficiency rickets requires replacement therapy with calcitriol. In Type II disease, resistance to calcitriol treatment may be so extreme that only very large supplements of calcium may be effective.[1,2] X-linked hypophosphataemic rickets is considered to be best treated with combined phosphate supplementation and calcitriol.[1,3] See also p.1390.

For further information on the agents mentioned above, see Calcium, p.1176 Vitamin D, p.1388 Phosphate, p.1181

1. Glorieux FH. Rickets, the continuing challenge. *N Engl J Med* 1991; **325**: 1875–7.
2. Hochberg Z, *et al.* Calcium therapy for calcitriol-resistant rickets. *J Pediatr* 1992; **121**: 803–8.
3. Verge CF, *et al.* Effects of therapy in X-linked hypophosphatemic rickets. *N Engl J Med* 1991; **325**: 1843–8.

For a discussion on the occurrence of rickets in small premature infants, and its treatment, see Rickets of Prematurity, p.1182.

Osteoporosis. Osteoporosis is a disorder of low bone mass;[1,2] it can affect most if not all of the skeleton but bone loss is more rapid in trabecular bone. There is an increase in bone fragility but patients are usually asymptomatic until fractures occur, most commonly in the spine, distal radius, or hip; patients may present with loss of height and back pain due to vertebral collapse.

Bone is continuously removed by osteoclasts (bone resorption) and replaced by osteoblasts (bone formation). Bone mass reaches a maximum at about 30 years of age and then gradually declines. Osteoporosis is therefore usually an age-related disease. It can affect both sexes, though women are at greater risk because there is an acceleration of bone loss after the menopause, particularly in a subgroup (about 35% of all women) of 'fast losers'. In addition, other factors can affect calcium and skeletal homoeostasis. For example, bone loss can be increased by medical disorders such as thyrotoxicosis, hypogonadism, and Cushing's syndrome, or by drugs such as the glucocorticoids (see p.1018). Also, immo-

Bone and Bone Disease continued

bility, especially in younger patients, can result in osteoblastic failure with an increase in osteoclastic resorption and the development of osteoporosis.

Prevention is the most effective method of dealing with osteoporosis as once bone mass has decreased it is difficult to replace. However, identifying those at most risk can be problematic, though the development of non-invasive techniques to measure bone mass[3] with improved methods of determining bone-turnover may lead to more accurate predictions and better diagnosis.[4] Should preventative measures not be taken or should they fail, then patients may not present until fractures are apparent as the disease is usually asymptomatic. A number of different approaches to the management of osteoporosis have been suggested, including changes in life-style, the use of drugs to decrease bone resorption such as calcium, oestrogens, calcitonins, and bisphosphonates, and the administration of pharmacological agents to stimulate bone formation, such as sodium fluoride.[2,5-9]

Prevention.[5-7,10] Initially, a modification of life-style is recommended. This includes avoiding smoking and alcohol (which have been associated with an increased risk of osteoporotic fracture), improving diet to ensure an adequate calcium intake, and increasing weight-bearing exercise.

In postmenopausal women, the most effective method of preventing osteoporosis is the administration of oestrogens (see p.1474). Oestrogen intervention slows or eliminates postmenopausal bone loss at all skeletal sites, particularly if given in the early years after menopause, and reduces the risk of fractures.[11,12] Efficacy is dependent on dose but the duration of therapy for maximum effect is unknown. It has been suggested that patients should be treated for as long as possible and for at least 5 to 10 years; there does not appear to be much residual effect when the oestrogen is withdrawn.[13] Women with an intact uterus must also be given progestogen therapy to reduce the risk of endometrial cancer, and the potential value of long-term administration of an oestrogen with a progestogen must be balanced against the risk of side-effects and the continuation of regular withdrawal bleeding.

If a deficiency of calcium or vitamin D is suspected, supplements would be expected to be of benefit in preventing the development of osteoporosis. Unfortunately, the calcium intake required by any individual cannot be easily determined and guidelines vary by country and culture. In the UK the reference nutrient intake (RNI) for adults is 700 mg per day;[14] in the USA the recommended dietary allowance (RDA) is 800 mg per day.[15] However, recent recommendations from the USA[16] have suggested higher intakes: 1 g daily in men up to 65 and in premenopausal women; the same amount in postmenopausal women receiving oestrogens and 1.5 g in those who do not; and 1.5 g daily in both sexes over the age of 65. A higher intake is also suggested in adolescents and young adults. Calcium supplements have been found to enhance the rate of increase in bone mineral density in prepubertal children; this could result in an increase in peak bone mass and reduce the future risk of osteoporosis.[17,18] In adults, the results of calcium supplementation (about 1 g of calcium daily by mouth) have been conflicting; some studies have reported a reduction in bone loss[19-21] but others have found calcium supplements to be of little benefit.[22,23] Any effect on the incidence of osteoporotic fractures is unclear. Irrespective of this controversy, in postmenopausal women oestrogen therapy is more effective than calcium supplementation[22] and remains the primary prophylactic treatment, although calcium supplementation may be given in addition.[20]

In patients in whom oestrogen therapy is inappropriate or contra-indicated, alternative agents such as the calcitonins or bisphosphonates may be considered.

Calcitonins have been found to prevent bone loss[24] but their use as prophylactic agents is limited by the necessity for parenteral administration. Intranasal spray formulations of salcatonin have been developed and have produced some beneficial effects.[25-27] Concomitant calcium supplementation is required. Bisphosphonates, which may be given by mouth, can also prevent bone loss.[28] The prolonged use of etidronate is restricted by the risk of osteomalacia but the newer bisphosphonates have less effect on bone mineralisation and may be more promising.

A number of other drugs have been reported to have favourable effects on bone mass including thiazide diuretics,[29,30] tamoxifen,[31] intermittent teriparatide,[32] progestogens,[33] and potassium bicarbonate.[34] However, their role, if any, in the prevention of osteoporosis has not yet been determined.

Treatment.[2,5-9] In patients with established osteoporosis, treatment is directed at maintaining bone mass. This involves many of the principles used for the prevention of bone loss (see above).

Oestrogens have been reported to stabilise or increase bone mass and to reduce the incidence of vertebral fractures in postmenopausal women with osteoporosis.[35] Hypogonadal men with osteoporosis should be treated with replacement doses of testosterone.[36,37]

Alternatively, calcitonins or bisphosphonates may be tried. Intranasal calcitonin administered daily with an oral calcium supplement has been found to increase the bone mineral content of the spine and to reduce the incidence of fractures in elderly women with moderate osteoporosis.[38] Calcitonin therapy may be particularly effective in women with high-turnover osteoporosis.[39] In addition, the analgesic effects of calcitonins may be advantageous in patients with acute pain due to osteoporotic fractures.[40] The bisphosphonate, disodium etidronate, has similar effects on bone mass and fractures in established osteoporosis to those of the calcitonins[41,42] but cannot be given for prolonged treatment because of the risk of osteomalacia; cyclical regimens of two weeks oral therapy alternating with 10 to 13 week rest periods (with calcium supplementation) have been used. However, doubts have been raised by the finding that during the third year of intermittent treatment with etidronate there appeared to be an increase in the number of fractures.[43]

Results of studies using the vitamin D substance calcitriol for the treatment of osteoporosis have been conflicting; although some have reported an increase in spinal bone density[44] and a reduction in the rate of new vertebral fractures,[45] others have found no significant effects.[46] However, antiresorptive agents are not generally considered to be very beneficial in patients over 75 years of age and in this group, in whom dietary deficiencies are common, calcium and vitamin D supplements can be the mainstay of treatment,[5,6,47] together with measures to reduce the risk of falls and protection of the patient from fractures should falls occur.[48]

Osteoporosis has also been treated with agents that promote bone formation. Fluoride stimulates osteoblasts and increases the density of trabecular bone. However, studies of sodium fluoride by mouth given with calcium have shown both a reduction in vertebral fractures[49-51] and an increase in nonvertebral fractures.[52] These different results may be attributed to the formulation, bioavailability, or dosage, better results having been achieved with low doses.[50,51] The use of sodium monofluorophosphate rather than sodium fluoride may give better results and fewer adverse effects.[8,53] Anabolic steroids have been tried but have considerable adverse effects. The use of growth factors or teriparatide (the 1-34 amino-acid fragment of human parathyroid hormone) to stimulate bone formation has been investigated; teriparatide administered as daily subcutaneous injections has been reported to increase selectively the trabecular bone density of the spine in osteoporotic patients.[54,55]

Ipriflavone, a flavonoid reported to have beneficial effects on bone resorption and formation, has produced promising responses in patients with established postmenopausal osteoporosis.[56]

For further information on the agents mentioned above, see

- Anabolic Steroids, p.1469
- Calcitonins, p.776
- Calcium, p.1176
- Disodium Etidronate, p.779
- Ipriflavone, p.1717
- Oestrogens, p.1471
- Potassium Bicarbonate, p.1173
- Progestogens, p.1476
- Sodium Fluoride, p.1752
- Sodium Monofluorophosphate, p.1754
- Tamoxifen, p.600
- Teriparatide, p.782
- Testosterone, p.1507
- Thiazides, p.887
- Vitamin D, p.1388

1. Dempster DW, Lindsay R. Pathogenesis of osteoporosis. *Lancet* 1993; 341: 797–801.
2. Peel N, Eastell R. Osteoporosis. *Br Med J* 1995; 310: 989–92.
3. Melton LJ, *et al.* Screening for osteoporosis. *Ann Intern Med* 1990; 112: 516–28.
4. Hansen MA, *et al.* Role of peak bone mass and bone loss in postmenopausal osteoporosis: 12 year study. *Br Med J* 1991; 303: 961–4
5. Riggs BL, Melton LJ. The prevention and treatment of osteoporosis. *N Engl J Med* 1992; 327: 620–7
6. Lindsay R. Prevention and treatment of osteoporosis. *Lancet* 1993; 341: 801–5.
7. Conference Report. Consensus Development Conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med* 1993; 94: 646–50.
8. Gennari C, *et al.* Management of osteoporosis and Paget's disease: an appraisal of the risks and benefits of drug treatment. *Drug Safety* 1994; 11: 179–95.
9. Eisman JA. Efficacy of treatment of osteoporotic fractures. *Am J Med* 1995; 98 (suppl 2A): 17S–23S.
10. Nelson ME, *et al.* Effects of high intensity strength training on multiple risk factors for osteoporotic fractures: a randomized controlled trial. *JAMA* 1994; 272: 1909–14.
11. Ettinger B. Prevention of osteoporosis: treatment of estradiol deficiency. *Obstet Gynecol* 1988; 72 (suppl): 12S–17S.
12. Genant HK, *et al.* Estrogens in the prevention of osteoporosis in postmenopausal women. *Am J Obstet Gynecol* 1989; 161: 1842–6.
13. Felson DT, *et al.* The effect of postmenopausal estrogen therapy on bone density in elderly women. *N Engl J Med* 1993; 329: 1141–6.
14. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
15. Subcommittee on the tenth edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council. *Recommended dietary allowances*. 10th ed. Washington, DC: National Academy Press, 1989.
16. NIH Consensus Development Panel on Optimal Calcium Intake. Optimal calcium intake. *JAMA* 1994; 272: 1942–8.
17. Johnston CC, *et al.* Calcium supplementation and increases in bone mineral density in children. *N Engl J Med* 1992; 327: 82–7.
18. Lloyd T, *et al.* Calcium supplementation and bone mineral density in adolescent girls. *JAMA* 1993; 270: 841–4.
19. Reid IR, *et al.* Effect of calcium supplementation on bone loss in postmenopausal women. *N Engl J Med* 1993; 328: 460–4. Correction. *ibid.*; 329: 1281.
20. Aloia JF, *et al.* Calcium supplementation with and without hormone replacement therapy to prevent postmenopausal bone loss. *Ann Intern Med* 1994; 120: 97–103.
21. Reid IR, *et al.* Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. *Am J Med* 1995; 98: 331–5.
22. Riis B, *et al.* Does calcium supplementation prevent postmenopausal bone loss? *N Engl J Med* 1987; 316: 173–7.
23. Orwoll ES, *et al.* The rate of bone mineral loss in normal men and the effects of calcium and cholecalciferol supplementation. *Ann Intern Med* 1990; 112: 29–34.
24. MacIntyre I, *et al.* Calcitonin for prevention of postmenopausal bone loss. *Lancet* 1988; i: 900–2.
25. Reginster JY, *et al.* 1-Year controlled randomised trial of prevention of early postmenopausal bone loss by intranasal calcitonin. *Lancet* 1987; ii: 1481–3.
26. Overgaard K, *et al.* Effect of salcatonin given intranasally on early postmenopausal bone loss. *Br Med J* 1989; 299: 477–9.
27. Reginster JY, *et al.* A 5-year controlled randomized study of prevention of postmenopausal trabecular bone loss with nasal salmon calcitonin and calcium. *Eur J Clin Invest* 1994; 24: 565–9.
28. Reginster JY, *et al.* Prevention of postmenopausal bone loss by tiludronate. *Lancet* 1989; ii: 1469–71.
29. Wasnich R, *et al.* Effect of thiazide on rates of bone mineral loss: a longitudinal study. *Br Med J* 1990; 301: 1303–5. Correction. *ibid.* 1991; 302: 218.
30. Cauley JA, *et al.* Effects of thiazide diuretic therapy on bone mass, fractures, and falls. *Ann Intern Med* 1993; 118: 666–73.
31. Love RR, *et al.* Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med* 1992; 326: 852–6.
32. Finkelstein JS, *et al.* Parathyroid hormone for the prevention of bone loss induced by estrogen deficiency. *N Engl J Med* 1994; 331: 1618–23.
33. Gallagher JC, *et al.* Effect of progestin therapy on cortical and trabecular bone: comparison with estrogen. *Am J Med* 1991; 90: 171–8.
34. Sebastian A, *et al.* Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med* 1994; 330: 1776–81.
35. Lufkin EG, *et al.* Treatment of postmenopausal osteoporosis with transdermal estrogen. *Ann Intern Med* 1992; 117: 1–9.
36. Anderson DC. Osteoporosis in men. *Br Med J* 1992; 305: 489–90.
37. Seeman E. The dilemma of osteoporosis in men. *Am J Med* 1995; 98 (suppl 2A): 76S–88S.
38. Overgaard K, *et al.* Effect of salcatonin given intranasally on bone mass and fracture rates in established osteoporosis: a dose-response study. *Br Med J* 1992; 305: 556–61.
39. Overgaard K, *et al.* Discontinuous calcitonin treatment of established osteoporosis—effects of withdrawal of treatment. *Am J Med* 1990; 89: 1–6.
40. Pun KK, Chan LWL. Analgesic effect of intranasal salmon calcitonin in the treatment of osteoporotic vertebral fracture. *Clin Ther* 1989; 11: 205–9.
41. Storm T, *et al.* Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. *N Engl J Med* 1990; 322: 1265–71.
42. Watts NB, *et al.* Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med* 1990; 323: 73–8.
43. Harris ST, *et al.* Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis: three years of blinded therapy followed by one year of open therapy. *Am J Med* 1993; 95: 557–67.
44. Gallagher JC, Goldgar D. Treatment of postmenopausal osteoporosis with high doses of synthetic calcitriol: a randomized controlled study. *Ann Intern Med* 1990; 113: 649–55.
45. Tilyard MW, *et al.* Treatment of postmenopausal osteoporosis with calcitriol or calcium. *N Engl J Med* 1992; 326: 357–62.
46. Ott SM, Chesnut CH. Calcitriol treatment is not effective in postmenopausal osteoporosis. *Ann Intern Med* 1989; 110: 267–74

47. Cagney MC, *et al.* Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *Br Med J* 1994; 308: 1081–2.
48. Lauritzen JB, *et al.* Effect of external hip protectors on hip fractures. *Lancet* 1993; 341: 11–13.
49. Mamelle N, *et al.* Risk-benefit ratio of sodium fluoride treatment in primary vertebral osteoporosis. *Lancet* 1988; ii: 361–5.
50. Nagant de Deuxchaisnes C, *et al.* Fluoride treatment of osteoporosis. *Lancet* 1990; 336: 48–9.
51. Pak CYC, *et al.* Slow-release sodium fluoride in the management of postmenopausal osteoporosis: a randomized controlled trial. *Ann Intern Med* 1994; 120: 625–32.
52. Riggs BL, *et al.* Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. *N Engl J Med* 1990; 322: 802–9.
53. Delmas PD, *et al.* Treatment of vertebral osteoporosis with disodium monofluorophosphate: comparison with sodium fluoride. *J Bone Miner Res* 1990; 5(suppl 1): S143–S147.
54. Slovik DM, *et al.* Restoration of spinal bone in osteoporotic men by treatment with human parathyroid hormone (1–34) and 1,25-dihydroxyvitamin D. *J Bone Miner Res* 1986; 1: 377–81.
55. Reeve J, *et al.* Treatment of osteoporosis with human parathyroid peptide and observations on effect of sodium fluoride. *Br Med J* 1990; 301; 314–18. Correction. *ibid.*; 477.
56. Agnusdei D, *et al.* Effects of ipriflavone on bone mass and bone remodeling in patients with established postmenopausal osteoporosis. *Curr Ther Res* 1992; 51: 82–91.

Paget's disease of bone. Paget's disease of bone (osteitis deformans) is characterised by excessive and disorganised bone resorption and formation. It may affect one or more bones, usually the cranium, spine, clavicles, pelvis, or long bones, but in most patients the majority of the skeleton is uninvolved. Paget's disease occurs in about 3 to 4% of the population over 40 years of age and its frequency increases with age. Patients are often asymptomatic. However, some patients may present with musculoskeletal and bone pain or with bone weakness and deformity that can result in fractures. Other features include hearing loss, nerve compression especially of the spinal cord, and, in severe disease, heart failure due to increased skeletal vascularity.

Many patients do not require any treatment. If bone pain occurs, initial management should be with nonsteroidal anti-inflammatory drugs. Drug therapy with agents that reduce bone resorption,[1-4] such as the calcitonins and bisphosphonates, may be indicated if bone pain is persistent or to prevent further progression of the disease, especially if complications such as spinal-cord compression are present. Such treatment is suppressive and while osteolytic lesions may be healed, the underlying disorder is not cured. Maximum relief is usually achieved within 6 months when therapy may then be withdrawn,[2] though symptoms do tend to recur and repeat courses may be required. Indefinite treatment may be necessary if there are severe complications such as vertebral collapse or neurological problems.

Calcitonins improve the symptoms of Paget's disease and can heal osteolytic lesions, though complete healing may take several years.[3] Doses are usually administered parenterally by subcutaneous or intramuscular injection either daily or 2 to 3 times a week. The subcutaneous route is favoured for self-administration but intranasal formulations are under investigation and may be more convenient.[5,6] Calcitonins, particularly those from animal sources, frequently elicit an antibody response and some patients develop resistance to therapy; this can often be overcome by changing to a calcitonin from a different species.[2,6]

Bisphosphonates also give symptomatic relief that can persist for several months after therapy has ceased but they do not appear regularly to heal osteolytic lesions. Most experience has been with disodium etidronate, which has the advantage that it may be given by mouth but unfortunately it also impairs bone mineralisation and can cause osteomalacia[7] especially with high doses or prolonged use. Etidronate is therefore usually given for periods of up to 6 months with drug-free intervals of at least 3 months; results of studies using high doses (20 mg per kg per day) but for shorter periods of time (up to 1 month) have differed[8,9] as to whether or not the benefits outweighed the adverse effects on bone mineralisation. Other bisphosphonates which have less effect on bone mineralisation, such as disodium clodronate[10,11] and disodium pamidronate,[12-14] have also been reported to be effective in Paget's disease of bone. Various regimens have been studied, including daily administration by mouth for several months, intermittent short courses given intravenously, and weekly intravenous infusions.

Concomitant administration of a calcitonin with a bisphosphonate has been reported to induce a better response than either agent given alone,[15] but some workers consider that such combinations should be reserved for patients only partially responsive to a single agent.[4] When administered consecutively, results have been conflicting;[16,17] treatment with a bisphosphonate followed by the calcitonin may be the preferred sequence.[16]

Plicamycin (mithramycin), a cytotoxic antibiotic with particular activity against osteoclasts, is highly effective in the treatment of Paget's disease of bone when administered daily by intravenous infusion for 5 to 10 days. However, it is associated with severe toxicity and is therefore now avoided[4] or reserved for patients refractory to other agents.[1,3,18]

Studies with gallium nitrate,[19-21] another inhibitor of bone resorption, have indicated beneficial effects in the treatment of Paget's disease of bone though the most effective and convenient dosage regimen has yet to be elucidated and the adverse effects assessed.

In selected patients, orthopaedic surgery such as hip replacement or correction of a bone deformity may be appropriate. Drug therapy with a calcitonin or bisphosphonate is usually given 1 to 3 months before surgery in order to reduce bone vascularity (thus minimising blood loss during the operation) and also to prevent development of postoperative hypercalcaemia of immobilisation.

For further information on the agents mentioned above, see
Calcitonins, p.776
Disodium Clodronate, p.779
Disodium Etidronate, p.779
Disodium Pamidronate, p.781
Gallium Nitrate, p.575
NSAIDs, p.72
Plicamycin, p.595

1. Stumpf JL. Pharmacologic management of Paget's disease. *Clin Pharm* 1989; 8: 485–95.
2. Hosking DJ. Advances in the management of Paget's disease of bone. *Drugs* 1990; 40: 829–40.
3. Stevenson JC. Paget's disease of bone. *Prescribers' J* 1991; 31: 98–103.
4. Gennari C, *et al.* Management of osteoporosis and Paget's disease: an appraisal of the risks and benefits of drug treatment. *Drug Safety* 1994; 11: 179–95.
5. Nagant de Deuxchaisnes C, *et al.* New modes of administration of salmon calcitonin in Paget's disease: nasal spray and suppository. *Clin Orthop* 1987; 217: 56–71.
6. Muff R, *et al.* Efficacy of intranasal human calcitonin in patients with Paget's disease refractory to salmon calcitonin. *Am J Med* 1990; 89: 181–4.
7. Boyce BF, *et al.* Focal osteomalacia due to low-dose diphosphonate therapy in Paget's disease. *Lancet* 1984; i: 821–4.
8. Preston CJ, *et al.* Effective short term treatment of Paget's disease with oral etidronate. *Br Med J* 1986; 292: 79–80
9. Gibbs CJ, *et al.* Osteomalacia in Paget's disease treated with short term, high dose sodium etidronate. *Br Med J* 1986; 292: 1227–9.
10. Yates AJP, *et al.* Intravenous clodronate in the treatment and retreatment of Paget's disease of bone. *Lancet* 1985; i: 1474–7.
11. Gray RES, *et al.* Duration of effect of oral diphosphonate therapy in Paget's disease of bone. *Q J Med* 1987; 64: 755–67.
12. Cantrill JA, *et al.* Low dose intravenous 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD) for the treatment of Paget's disease of bone. *Ann Rheum Dis* 1986; 45: 1012–18.
13. Harinck HIJ, *et al.* Paget's disease of bone: early and late responses to three different modes of treatment with aminohydroxypropylidene bisphosphonate (APD). *Br Med J* 1987; 295: 1301–5.
14. Anderson DC, Cantrill JC. Treatment of Paget's disease of bone. *Br Med J* 1988; 296: 291.
15. O'Donoghue DJ, Hosking DJ. Biochemical response to combination of disodium etidronate with calcitonin in Paget's disease. *Bone* 1987; 8: 219–25.
16. Perry HM, *et al.* Alternate calcitonin and etidronate disodium therapy for Paget's bone disease. *Arch Intern Med* 1984; 144: 929–33.
17. Rico H, *et al.* Biochemical assessment of acute and chronic treatment of Paget's bone disease with calcitonin and calcium with and without biphosphonate. *Bone* 1988; 9: 63–6.
18. Ryan WG, *et al.* Apparent cure of Paget's disease of bone. *Am J Med* 1990; 89: 825–6.
19. Matkovic V, *et al.* Use of gallium to treat Paget's disease of bone: a pilot study. *Lancet* 1990; 335: 72–5.
20. Warrell RP, *et al.* Gallium nitrate for advanced Paget disease of bone: effectiveness and dose-response analysis. *Ann Intern Med* 1990; 113: 847–51.
21. Bockman RS, *et al.* A multicenter trial of low dose gallium nitrate in patients with advanced Paget's disease of bone. *J Clin Endocrinol Metab* 1995; 80: 595–602.

Renal osteodystrophy. Renal osteodystrophy is a complex condition associated with chronic renal failure which involves the development of osteitis fibrosa (hyperparathyroid bone disease) and osteomalacia.[1,2] Osteosclerosis and osteoporosis may also occur.

Vitamin D is metabolised in the kidney to its most active form, 1,25-dihydroxycholecalciferol, and during renal disease a reduction in the synthesis of this metabolite results in reduced intestinal absorption of calcium, and hypocalcaemia. In addition, a reduction in the renal excretion of phosphate leads to hyperphosphataemia which exacerbates these changes and increases the risk of soft tissue and vascular calcification.

The result is inadequate bone mineralisation with the development of osteomalacia (see p.773) and excessive production of parathyroid hormone, resulting in secondary hyperparathyroidism (see p.776). Hyperparathyroidism increases bone turnover and leads to osteitis fibrosa, a condition characterised by an abundance of osteoclasts, osteoblasts, and osteocytes, and the deposition of fibrous tissue in the bone marrow.

In patients with chronic renal failure, the accumulation of aluminium from either the dialysis water supply or from the use of aluminium-containing phosphate binders may also have adverse effects on bone (see Aluminium Hydroxide, p.1203).

Most patients are asymptomatic at presentation and treatment is aimed at controlling the plasma concentrations of calcium, phosphate, and parathyroid hormone.[2] Severe hyperphosphataemia should be corrected first to reduce the risk of metastatic calcification which may be aggravated by the use of vitamin D compounds which increase calcium absorption.

Hyperphosphataemia is initially controlled with a low-phosphate diet but many patients, especially those on dialysis, also need an oral phosphate binder to complex with dietary phosphate in the gastro-intestinal tract and reduce its absorption.[2,3]

Calcium salts such as the carbonate or acetate are effective phosphate binders and have been found to suppress hyperparathyroidism;[4,5] 2.5 to 17 g of calcium carbonate daily has been given[5] in divided doses with meals but careful individual adjustment of the dose is required depending on the dietary intake of phosphate and the plasma-phosphate concentration. Calcium salts also raise plasma-calcium concentrations and combat acidosis but hypercalcaemia can occur;[6,7] the use of dialysis fluids with a lower calcium content has been suggested for these patients.[2,8]

Alternatively, aluminium hydroxide may be given but relatively large doses are required and aluminium toxicity has been reported in some patients with compromised renal function (see Aluminium Hydroxide, p.1203). Long-term use is not generally recommended.[2] Other compounds that have been reported to be effective phosphate binders include sucralfate[9,10] (an aluminium-containing compound) and magnesium carbonate.[11]

Vitamin D compounds that do not require renal hydroxylation such as calcitriol (1,25-dihydroxycholecalciferol) or its synthetic analogue, alfacalcidol, are the drugs of choice for correcting the hypocalcaemia and also contribute to the control of secondary hyperparathyroidism;[2] calcium supplements may also occasionally be required. Administration of alfacalcidol in the early stages of renal failure, before dialysis was required, has also been reported to improve subclinical bone disease.[12] Calcitriol or its analogues are administered by mouth; the dose is adjusted according to response but must be carefully monitored as the dose required for adequate suppression of parathyroid hormone secretion may be close to that which causes hypercalcaemia. It has also been recommended that a close watch should be kept on renal function since deterioration may be accelerated by calcitriol, an effect that may be independent of any induced hypercalcaemia.[13] Patients unresponsive to drug treatment or who develop hypercalcaemia (which may itself accelerate the decline in renal function) may require sub-total parathyroidectomy.[1,2] Alternatively, the administration of calcitriol as intermittent intravenous infusions (3 times a week during haemodialysis) has been reported to be effective in reducing plasma concentrations of parathyroid hormone and ameliorating osteitis fibrosa in some patients with moderate to severe secondary hyperparathyroidism due to chronic renal failure who had failed to respond adequately to oral calcitriol.[14]

For further information on the agents mentioned above, see
Aluminium Hydroxide, p.1203
Calcium Acetate, p.1176
Calcium Carbonate, p.1208
Calcium, p.1176
Magnesium Carbonate, p.1225
Sucralfate, p.1243
Vitamin D, p.1288

1. Malluche HH, Faugere M-C. Renal osteodystrophy. *N Engl J Med* 1989; 321: 317–19.
2. Gower P. Prevention of bone disease in chronic renal failure. *Prescribers' J* 1992; 32: 245–51.
3. Coburn JW, Salusky IB. Control of serum phosphorus in uremia. *N Engl J Med* 1989; 320: 1140–42.

Bone and Bone Disease continued

4. Mak RHK, *et al.* Suppression of secondary hyperparathyroidism in children with chronic renal failure by high dose phosphate binders: calcium carbonate versus aluminium hydroxide. *Br Med J* 1985; **291:** 623–7.
5. Slatopolsky E, *et al.* Calcium carbonate as a phosphate binder in patients with chronic renal failure undergoing dialysis. *N Engl J Med* 1986; **315:** 157–61.
6. Stein HD, *et al.* Calcium carbonate as a phosphate binder. *N Engl J Med* 1987; **316:** 109–10.
7. Raine AEG, Oliver DO. Management of hyperphosphataemia in renal dialysis patients. *Lancet* 1987; **i:** 633–4.
8. Slatopolsky E, *et al.* Calcium carbonate as a phosphate binder. *N Engl J Med* 1987; **316:** 110.
9. Leung ACT, *et al.* Aluminium hydroxide versus sucralfate as a phosphate binder in uraemia. *Br Med J* 1983; **286:** 1379–81.
10. Vucelić B, *et al.* Changes in serum phosphorus, calcium and alkaline phosphatase due to sucralfate. *Int J Clin Pharmacol Ther Toxicol* 1986; **24:** 93–6.
11. O'Donovan R, *et al.* Substitution of aluminium salts by magnesium salts in control of dialysis hyperphosphataemia. *Lancet* 1986; **i:** 880–2.
12. Hamdy NAT, *et al.* Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure. *Br Med J* 1995; **310:** 358–63.
13. Chan JCM, *et al.* A prospective, double-blind study of growth failure in children with chronic renal insufficiency and the effectiveness of treatment with calcitriol versus dihydrotachysterol. *J Pediatr* 1994; **124:** 520–8.
14. Andress DL, *et al.* Intravenous calcitriol in the treatment of refractory osteitis fibrosa of chronic renal failure. *N Engl J Med* 1989; **321:** 274–9.

Hypercalcaemia

The management of hypercalcaemia is discussed on p.1170 where bisphosphonates, especially disodium pamidronate, are considered to be the treatment of choice once the patient has been adequately rehydrated.

Parathyroid Disorders

Parathyroid hormone, secreted by the parathyroid gland, maintains concentrations of ionised calcium in extracellular fluid within normal limits. It acts directly on the kidney to enhance renal reabsorption of calcium, to increase phosphate excretion, and to promote the conversion of vitamin D to its active metabolite, 1,25-dihydroxycholecalciferol, which in turn, enhances calcium absorption from the gastrointestinal tract. Parathyroid hormone also acts on bone, to accelerate bone resorption and the release of calcium and phosphate into the extracellular fluid. Secretion of parathyroid hormone is primarily regulated by the extracellular concentration of ionised calcium; hypocalcaemia stimulates secretion whereas hypercalcaemia has an inhibitory effect. 1,25-Dihydroxycholecalciferol can also suppress parathyroid hormone secretion.

Disorders of parathyroid hormone secretion cause a disruption of calcium homoeostasis and in the long-term, may result in bone disease.

Hyperparathyroidism. Primary hyperparathyroidism is a disorder of parathyroid hormone hypersecretion usually caused by adenomas or hyperplasia of the parathyroid glands. Patients are commonly asymptomatic but may have signs of hypercalcaemia (p.1170); nephrolithiasis may also be present. Secondary hyperparathyroidism occurs in response to hypocalcaemia as in chronic renal failure and if prolonged may progress to autonomous hypersecretion by the parathyroid gland (tertiary hyperparathyroidism).

Severe hypercalcaemia may require immediate treatment (see p.1170). In the long-term, the treatment of choice for primary and tertiary hyperparathyroidism is usually surgical parathyroidectomy but in patients with asymptomatic primary hyperparathyroidism no therapy may be necessary.[1]

The value of drug treatment is less well defined. Oral phosphate supplements have been given in the short-term to alleviate hypercalciuria and hypercalcaemia.[2] Bisphosphonates can be used to inhibit bone resorption,[2] but their role in the management of hyperparathyroidism has yet to be determined. Disodium etidronate has been tried[3] but may cause osteomalacia after prolonged administration. In preliminary studies, disodium clodronate has reduced hypercalcaemia[4-6] but has failed to achieve complete normalisation of plasma-calcium concentrations and in some patients the effect was only transient. Oestrogens have been reported to reduce the rate of bone turnover and plasma-concentrations of calcium in postmenopausal women with primary hypoparathyroidism,[7,8] but any long-term benefits are uncertain.[9]

The treatment of secondary hyperparathyroidism is usually aimed at the underlying cause of the hypocalcaemia; for example, for the treatment of secondary hyperparathyroidism associated with chronic renal disease, see Renal Osteodystrophy, p.775.

For further information on the agents mentioned above, see
Disodium Clodronate, p.779
Disodium Etidronate, p.779
Oestrogens, p.1471
Phosphate, p.1181

1. Consensus Development Conference Panel. Diagnosis and management of asymptomatic primary hyperparathyroidism: consensus development conference statement. *Ann Intern Med* 1991; **114:** 593–7.
2. Anonymous. Medical management of primary hyperparathyroidism. *Lancet* 1984; **ii:** 727–8.
3. Licata AA, O'Hanlon E. Treatment of hyperparathyroidism with etidronate disodium. *JAMA* 1983; **249:** 2063–4.
4. Shane E, *et al.* Effects of dichloromethylene diphosphonate on serum and urinary calcium in primary hyperparathyroidism. *Ann Intern Med* 1981; **95:** 23–7.
5. Douglas DL, *et al.* Drug treatment of primary hyperparathyroidism: use of clodronate disodium. *Br Med J* 1983; **286:** 587–90.
6. Hamdy NAT, *et al.* Clodronate in the medical management of hyperparathyroidism. *Bone* 1987; **8** (suppl 1): 869–77.
7. Marcus R, *et al.* Conjugated estrogens in the treatment of postmenopausal women with hyperparathyroidism. *Ann Intern Med* 1984; **100:** 633–40.
8. Selby PL, Peacock M. Ethinyl estradiol and norethindrone in the treatment of primary hyperparathyroidism in postmenopausal women. *N Engl J Med* 1986; **314:** 1481–5.
9. Coe FL, *et al.* Is estrogen preferable to surgery for postmenopausal women with primary hyperparathyroidism? *N Engl J Med* 1986; **314:** 1508–9.

Hypoparathyroidism. Hypoparathyroidism occurs when there is a deficiency of parathyroid hormone secretion due to lack of parathyroid gland development or destruction of the gland, for example by autoimmune disease or surgical removal. Other factors that may lead to a deficiency in parathyroid hormone include hypomagnesaemia and parathyroid adenomas. Where the deficiency results from resistance to parathyroid hormone the condition is termed pseudohypoparathyroidism. Hypoparathyroidism leads to hypocalcaemia and hyperphosphataemia, though in some patients these may not become significant until there is an increased calcium demand as in pregnancy.

Treatment is aimed at correcting the hypocalcaemia; in patients with hypocalcaemic tetany the parenteral administration of calcium salts may be necessary. In the long-term, treatment is usually with oral vitamin D compounds which increase the intestinal absorption of calcium; calcium supplements may be required if dietary calcium is inadequate. Calcium concentrations and renal function require careful monitoring, especially since the lack of parathyroid hormone results in an increase in the renal excretion of calcium and the risk of nephrolithiasis. Beneficial effects on plasma-calcium concentrations have been reported following the use of thiazide diuretics to reduce the urinary excretion of calcium.[1,2] However, these effects tended to be modest and thiazide diuretics have not been found to be effective in all patients with hypoparathyroidism;[3] adverse effects such as metabolic alkalosis may also be a problem.[4]

In one patient with postsurgical hypoparathyroidism good results have been reported following transplantation of parathyroid cells depleted of antigen-bearing cells.[5] It was considered that this might prove a promising technique in the future.

For further information on the agents mentioned above, see
Calcium, p.1176
Thiazides, p.887
Vitamin D, p.1388

1. Porter RH, *et al.* Treatment of hypoparathyroid patients with chlorthalidone. *N Engl J Med* 1978; **298:** 577–81.
2. Newman GH, *et al.* Effect of bendrofluazide on calcium reabsorption in hypoparathyroidism. *Eur J Clin Pharmacol* 1984; **27:** 41–6.
3. Gertner JM, Genel M. Chlorthalidone for hypoparathyroidism. *N Engl J Med* 1978; **298:** 1478.
4. Barzel US. Chlorthalidone for hypoparathyroidism. *N Engl J Med* 1978; **298:** 1478.
5. Decker GAG, *et al.* Allotransplantation of parathyroid cells. *Lancet* 1995; **345:** 124. Correction. *ibid.*: 464.

Alendronic Acid (4537-w)

Alendronic Acid (*BAN, rINN*).

AHButBP; Aminohydroxybutylidene Diphosphonic Acid; G-704650 (monosodium alendronate); L-670452 (monosodium alendronate); MK-217 (monosodium alendronate); MK-0217(monosodium alendronate) 4-Amino-1-hydroxybutane-1,1-diylbis(phosphonic acid).

$C_4H_{13}NO_7P_2$ = 249.1.

CAS — 66376-36-1 (alendronic acid); 121268-17-5 (monosodium alendronate).

NOTE. Alendronate Sodium is *USAN*.

Alendronic acid is used as an alendronate salt, a bisphosphonate with the general properties of disodium etidronate (see p.779) but reportedly a greater potency. It inhibits bone resorption and has been given by intravenous infusion or by mouth in the treatment of diseases associated with excessive bone turnover such as Paget's disease of bone and osteoporosis and also in the treatment of bone metastases.

The dose of alendronate sodium for osteoporosis in postmenopausal women is equivalent to 10 mg of alendronic acid daily by mouth at least 30 minutes before food.

Bisphosphonates are widely used in the treatment of Paget's disease of bone—see p.775, and have been employed in the management of osteoporosis—p.773, and in the management of bone metastases—p.524.

References to the use of alendronate are given below:

1. Adami S, *et al.* Treatment of Paget's disease of bone with intravenous 4-amino-1-hydroxybutylidene-1,1-bisphosphonate. *Calcif Tissue Int* 1986; **39:** 226–9.
2. Attardo-Parrinello G, *et al.* Effects of a new aminodiphosphonate (aminohydroxybutylidene diphosphonate) in patients with osteolytic lesions from metastases and myelomatosis: comparison with dichloromethylene diphosphonate. *Arch Intern Med* 1987; **147:** 1629–33.
3. Harris ST, *et al.* The effect of short term treatment with alendronate on vertebral density and biochemical markers of bone remodeling in early postmenopausal women. *J Clin Endocrinol Metab* 1993; **76:** 1399–1406.
4. Chesnut CH, *et al.* Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. *Am J Med* 1995; **99:** 144–52.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations

UK: Fosamax.

Calcitonins (12106-w)

Endogenous calcitonin is a polypeptide hormone involved in the regulation of calcium and bone metabolism. Forms used therapeutically include: calcitonin (pork), extracted from pig thyroid; a synthetic human calcitonin; elcatonin, a synthetic analogue of eel calcitonin; and salcatonin, a synthetic salmon calcitonin. They all have the property of lowering plasma-calcium concentrations by diminishing the rate of bone resorption and are used in Paget's disease of bone, hypercalcaemia, osteoporosis, and metastatic bone pain. Calcitonins are generally given by subcutaneous or intramuscular injection.

Adverse effects with calcitonins include gastrointestinal disturbances, flushing, and tingling; these are more common at the beginning of treatment.

Calcitonin (Human) (11091-e)

Calcitonin-human; Human Calcitonin.

$C_{151}H_{226}N_{40}O_{45}S_3.3HCl$ = 3527.3.

Pharmacopoeias. In *Swiss*.

A synthetic polypeptide comprising 32 amino acids in the same linear sequence as in naturally occurring human calcitonin.

Calcitonin (Pork) (8053-f)

Calcitonin (Pork) (*BANM*).

CAS — 12321-44-7.

NOTE. The synonym thyrocalcitonin and the CAS number 9007-12-9 have been used for calcitonin that is often of pork origin.

Pharmacopoeias. In *Br.* and *It.*

A polypeptide hormone obtained from pork thyroid. The B specifies not less than 60 units per mg calculated with reference to the dried substance. Trace amounts of thyroid hormones may be present. The BP limits are not more than 20 n of liothyronine and not more than 50 ng of thyroxine per mg of calcitonin.

CERTIFICATE OF SERVICE

I hereby certify that on May 11, 2005, I caused two copies of the foregoing BRIEF AND ADDENDUM FOR APPELLEE DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE to be sent overnight delivery to:

Courtenay C. Brinckerhoff, Esq.
Foley & Lardner LLP
3000 K Street, N.W. Suite 500
Washington, D.C. 20007
(202) 295-4094

Heather F. Auyang
Associate Solicitor